Assessment of older patients in oncology

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ABSTRACT

Cancer is a disease of the elderly with almost 60% of new cancer diagnoses and 70% of cancer deaths occurring in patients over 65 years of age. With population ageing the prevalence of cancer in older patients is expected to rise even further in the future. Choosing the optimal treatment for older cancer patients is challenging since ageing is often related with physiological changes and organ function impairment that can alter anticancer treatment tolerance and efficacy. Ageing is a highly individualized process and chronological age alone cannot accurately define the functional reserve and life expectancy of an individual. A number of methods have been developed for a thorough assessment of older patients in order to help treatment decisions. The comprehensive geriatric assessment of older patients in oncology is presented in this article.

Key words: elderly; cancer; geriatric; assessment.

INTRODUCTION

Although more than half of new cancers occur in the elderly [1], elderly patients are underrepresented in the large randomized trials [2-4], thus limiting applicability of these trials' conclusions on the general elderly population. It is well-recognized that aging is a heterogeneous process and, furthermore, performance status (PS) alone cannot describe the functional status and commonly existing comorbidities in the elderly [5]. Geriatricians have validated standardized tools for assessment of "functional status" as distinct from chronological age, looking for signs of accelerated aging that increase vulnerability to disablement and mortality. These geriatric perspectives have been merged in oncology and it is now recommended that a more thorough and multidimensional evaluation of older cancer patients should be performed in order to better define biological age and individualize treatment in this patient population [6-9]. This multidimensional assessment, often referred to as comprehensive geriatric assessment (CGA) in geriatric oncology literature, includes a compilation of reliable and valid tools to assess geriatric domains such as comorbidity, functional-, cognitive-, psychological- and nutritional status, physical performance, medication review and social support. The tools commonly used within the CGA to evaluate a geriatric cancer patient are summarized in Table 1.

Based on CGA results, four taxonomic groups of older individuals may be defined with different life expectancy, rehabilitative potential and presumed stress tolerance [10] (Table 2). Those in very good condition, labeled "fit", may receive the same treatment as younger patients; those partially impaired, labeled "vulnerable", may require tailored approach and moderate assistance; while the "frail" ones are candidates only for supportive care; and the last category includes those in critical condition, labeled "very frail" or "near death".

FUNCTIONAL ASSESSMENT

The traditional method for functional status assessment in cancer patients is PS. The scales most often used for PS assessment are the Karnofsky Performance Status (KPS) [11] and the Eastern Cooperative Oncology Group (ECOG) score [12]. However, in geriatrics these scales are not considered adequate for an accurate functional assessment and a more extensive evaluation is required [13]. Two methodological approaches for the functional assessment of older patients have been developed. The first method uses questionnaires which describe several activities, patients answer whether they are ca-

Table 1.
Comprehensive geriatric assessment

Comprehensive Geriatric Assessment elements	
Domain	**Instruments used – parameters examined**
Function	Activities of Daily Living (ADL) [15] Instrumental Activities of Daily Living (IADL) [19] "Timed Up and Go" [26]
Comorbidity	Charlson index score [31] Cumulative Illness Rating Scale-Geriatric [33]
Cognitive	Mini Mental State Examination (MMSE) [53]
Emotional	Geriatric Depression Scale-15 (GDS-15) [58]
Nutrition	Mini Nutritional Assessment [42, 44]
Geriatric syndromes	Dementia, delirium, depression, incontinence, osteoporosis with bone fractures, falls, neglect and/or abuse, failure to thrive
Polypharmacy	Number and appropriateness of medications, risk of drug interaction
Socioeconomic status	Economic independence, presence of a reliable caregiver

Table 2.
Taxonomy of elderly patients according to comprehensive geriatric assessment (CGA)

Taxonomy group	CGA parameters	Therapeutic approach
Group 1: "Fit"	No ADL or IADL dependence No severe comorbidity No geriatric syndromes present	Treat as younger patients
Group 2: "Vulnerable"	IADL but no ADL dependence Stable comorbidity No geriatric syndromes present Mild cognitive disorders	Tailored treatment Rehabilitation measures
Group 3: "Frail"	ADL dependence Severe or unstable comorbidity Presence of geriatric syndromes	Supportive care
Group 4: "Very frail"	Critical condition - near death	

pable of performing said activities [14] and it mainly involves evaluation of activities of daily living (ADL) and instrumental activities of daily living (IADL) [7]. ADL include activities that are essential for patients to maintain independence at home and include ability to bathe, feed oneself, dress oneself, maintain continence, use the toilet and functional transfer. The basic scale used for ADL assessment is the Katz scale [15]. ADL assessment has been proved to be a good prognostic factor in older patients in general (not specifically cancer patients) and is strongly associated with one- and two-year mortality following hospital admission [16, 17]. Another study revealed functional status as a stronger predictor of length of stay, mortality, and nursing home placement than principal admitting diagnosis [18]. IADL assessment includes more advanced self-care activities such as the ability to prepare meals, do housework, use the telephone, take medications, manage one's finances and use transportation means [19]. In oncology, IADL dependence has been associated with poorer survival in lung cancer [20] and acute myeloid leukemia patients [21], with increased risk of chemotherapy toxicity in ovarian cancer patients [22] and with higher risk for postoperative complications in older patients undergoing surgical operation [23]. Furthermore, IADL dependence was associated with inferior survival in prospective studies that included patients over 70 years of age with solid tumors [24] and hematological malignancies [25].

The second method of measuring functional status involves having the patient perform some specific activities under physician observation in order to examine what he/she is actually capable of doing. A commonly used tool is the

"Timed Up and Go" tool (measures speed during several functional maneuvers, which include standing up, walking, turning and sitting down) [26]. However, direct functional assessment only moderately correlates with ADL scores and discordance between questionnaire-based and direct functional assessment has been reported [27].

ASSESSMENT OF COMORBIDITY

Older patients present with increased concomitant diseases. Furthermore, comorbidity does not appear to correlate closely with either tumor stage or functional status [5]. Therefore, comorbidity should be assessed independently. Comorbidity may influence cancer patients in many aspects, such as treatment decision, treatment tolerance and finally cancer prognosis [28]. There are only a few clinical trials that incorporate assessment of comorbidity and so it is difficult to define the exact role in each aspect of cancer management [29, 30].

There are many validated tools available to measure comorbidity and each has specific characteristics and differences regarding its easiness of use and validity in measuring comorbidity. Among them, oncology authors most frequently use (in different settings) the Charlson Index [31]; the Cumulative Illness Rate Scale [32] with the Geriatric module (CIRS-G) [33]; the Kaplan-Feinstein Index [34]; and the Adult Comorbidity Evaluation 27 (ACE-27) [35], with Charlson and CIRS-G being the most widely used [36]. The use of validated tools for measuring comorbidity should be preferred instead of general lists of diseases in order to better reproduce and compare the data among different studies.

The Charlson Comorbidity Index

The Charlson Comorbidity Index [31] is a scale with 19 diseases weighted from one to six points. The total score is valid in predicting mortality risk over a period of a few weeks to 10 years and has also been validated in older cancer patients [5]. Potential limitations in oncology include the fact that the index ignores several comorbidities that may be relevant in designing the treatment of cancer patients, such as hematopoietic disorders other than malignancies, polyneuropathy or moderate renal dysfunction. The rating criteria are well defined in the appendix of the original paper [31] and fairly easy for frequent users to memorize.

The Cumulative Illness Rating Scale

The CIRS is aimed at a comprehensive recording of all the comorbid diseases of a patient. Its principle is to classify comorbidities by organ system affected, and rate them according to their severity from 0 to 4, in a way similar to the Common Toxicity Criteria grading (none, mild, moderate, severe, extremely severe/life-threatening). An adaptation that is particularly interesting for geriatric oncologists is the CIRS-Geriatric (CIRS-G) designed by Miller and colleagues, with a multidisciplinary designed rating manual aimed at a geriatric population (and, therefore, detailing several geriatric problems in the list) [33].

NUTRITIONAL STATUS

There are several reports demonstrating the adverse impact of weight loss or low body mass index (BMI) in the general older population [37-39]. Cancer may affect consumption and assimilation of food in many different ways. This is of great importance for older individuals whose functional or financial limitations along with depressed mood may further worsen their capability to maintain adequate caloric intake. The deleterious effect of weight loss on survival was demonstrated in a study of 3047 patients enrolled in 12 ECOG chemotherapy protocols [40]. In this analysis, weight loss was associated with a lower performance status and was an independent prognostic factor for survival. Furthermore, it was associated with a decrease in chemotherapy response rates in women with breast cancer, although this correlation was not present in other tumor types. Even a limited weight loss (0 to 5 percent) can be clinically significant in cancer patients.

The assessment of nutritional state should be a relevant part of CGA, given its numerous implications with tumor prognosis, tolerance to surgery and radio-chemotherapeutic measures, risk of infections, management of comorbidities and most importantly, quality of life [41]. Calculating body mass index (the weight in kilograms divided by the square of height in meters) is an easy and well-known method of monitoring weight in adult populations, with the normal range of 20 (or 18.5 according to the WHO) to 24.9 kg/m^2. However, this parameter has been used mainly to assess prevalence and consequences of obesity rather than to evaluate malnourishment. Some laboratory parameters such as hemoglobin, albumin, transferrin, cholesterol and C-Reactive Protein (CRP) have been proposed as indicators of malnutrition. Unfortunately, in cancer patients, they could hardly be used to follow prospectively the compliance to dietary prescriptions because they may be affected by organ dysfunction as well as by metabolic and immunological deregulation induced by cancer-released cytokines and chemotherapy.

The use of the mini-nutritional assessment (MNA) [42] instrument can better assess nutritional status and identify patients at risk of malnutrition compared with the proportional weight loss [43]. The MNA is an 18-item questionnaire originally validated for use in elderly patients with non-malignant diseases. The instrument is available on-line [44] and should be incorporated in geriatric oncology prospective studies.

GERIATRIC SYNDROMES

An important issue in geriatric oncology is the presence of the so-called "geriatric syndromes" (GS). The definition of this

term includes clinical conditions which appear in the elderly and cannot be classified into discrete disease categories. Common GS are dementia, delirium, depression, falls, neglect and abuse, spontaneous bone fractures and failure to thrive. [45]. Sometimes the presence of GS may complicate cancer treatment, while the side-effects of cancer treatment can worsen underlying GS [46], thus negatively affecting the quality of life of elderly cancer patients. The incidence of GS in elderly cancer population is high ranging from 34% to 51% of patients with different cancer types [47].

Dementia

Dementia is defined as the impairment of two or more fields of cognitive function. These fields are memory, judgment, information recognition and recall. The most common types of dementia are Alzheimer's disease, vascular- and mixed dementia [46]. Dementia may also appear as a result of cancer treatment [48, 49].

Delirium

Delirium is defined as the acute decline in attention and in overall cognitive function which develops in a short time period and fluctuates. The incidence of delirium in outpatients is estimated to be of 10-24% and in inpatients of about 25-60% [46, 50-52]. In 66-76% of patients delirium is unrecognized [51]. It is often difficult to differentiate between dementia and delirium. Whether cancer patients with cognitive function impairment are able to give informed consent is an issue of debate.

The most commonly cognitive function assessment tool is the *Mini-Mental Status Exam* (MMSE). The MMSE constitutes of a 30 points scale which evaluates time, orientation, attention, calculation, naming, reading, writing and drawing [53].

Depression

Depression is the most frequently present syndrome in cancer patients and is related with decreased overall survival [54, 55]. In general, about 25% of medically ill geriatric patients will develop depression [56]. However, it is often unrecognized by oncologists. One of the main reasons for this phenomenon is the appearance of symptoms like anorexia, weight loss, sleep disorders, energy loss, death thoughts and suicide attempts which could appear either due to depression or the tumor [57].

The Geriatric Depression Scale-15 (GDS-15) is a validated tool for assessing depression. It comprises a clinical rating scale with 15 yes/no answers and is one of the most commonly used instruments for screening cognitively intact older adults [58].

Falls

Falls constitute a significant problem occurring in elderly population which might lead to injuries and hospitalization [45]. Published studies report that about 30-40% of elderly people over 65 years of age suffer from falling [59]. Geriatric cancer patients usually develop symptoms like fatigue and dizziness which significantly increase the risk of falls. Symptoms like these might be also side-effects of cancer therapies. Fall-related fractures are consistent with high healthcare costs and generally, falls prevention programs seem to be cost-effective [60].

FRAILTY

Frailty in the elderly can generally be described as a product of "excess demand imposed upon reduced capacity" [61]. Frail elderly patients have a decreased ability to maintain homeostasis in times of acute stress due to reduced reserves in multiple organ systems. The syndrome is manifested with loss of skeletal muscle mass, abnormal function in inflammatory/neuroendocrine systems, and poor energy regulation [62]. Despite the fact that frailty establishes itself gradually, once the elderly become frail, there is a progressive downward spiral toward failure to thrive and death [63]. The incidence of frailty is reported to be from 2% to 7% between the ages of 65 to 75 years, and increases with age [64]. This percentage increases to 25% for elderly persons in their 80's [65] and is considerably higher among women [66]. According to the Fried definition, which is the most widely accepted, frailty is described as a clinical syndrome in which 3 or more of the following criteria were present: unintentional weight loss (10lbs in past year), self-reported exhaustion, weakness (grip strength), slow walking speed, and low physical activity.

In geriatric oncology, the definition of frailty syndrome may be extremely useful for estimating the risk of side-effects, especially for old or very old patients who are apparently physically active and cognitively intact [67]. Intervention on frailty may minimize the risk of toxicity and substantially improve the prognosis of older cancer patients.

PHARMACOLOGICAL ASPECTS

The term pharmacokinetics describes the course of a certain drug in the body. It includes absorption, distribution across body compartments, metabolism and excretion. Aging results in reduced enzymatic activity and prolongs the process of metabolism and excretion for many drugs with accumulation of their toxic metabolites.

Absorption. Changes in drug absorption are generally mild and probably not clinically relevant. They stem from decrease in the small bowel absorptive area and changes in gastric pH.

Distribution. Changes in the fat and water composition in favor of the former result in increased distribution of highly lipophilic drugs and increased half-life times. Reduced levels of albumin may increase the levels of active compounds due to increased proportion of free unbound drugs.

Hepatic metabolism. Overall, the enzymatic activity of cyto-

chrome P-450 system decreases with age, typically by 30-40% [68], and as such drug doses should be decreased proportionally. On the other hand, clearance by conjugation (e.g. glucuronization) is usually unaffected by age.

Renal elimination. Age results in decrease both in glomerular and tubular function and the use of drugs with primary elimination by the kidneys should be guided by creatinine clearance estimation formulas rather than serum creatinine concentration alone. The latter can be within normal limits despite a decreased glomerular filtration rate due to sarcopenia often present in older individuals.

Although there are no specific prescription guidelines for elderly patients, special care should be given to drug interactions. The elderly usually take many drugs for various medical pre-existing conditions and polypharmacy is quite common nowadays. Drug interactions may occur when prescribed drugs share the same metabolic and excretion systems and also due to pharmacodynamics issues [69].

SHORT SCREENING TOOLS

In routine clinical practice the use of the full Comprehensive Geriatric Assessment (CGA) faces several difficulties. A much more practical and cost-effective approach is to use shorter screening tools. Ideally, these tools could allow the identification of fit patients for whom the complete CGA would not identify relevant age-related problems, while patients with impairment would proceed further to a full multidisciplinary CGA [13].

The *VES-13* is a self-administered questionnaire that consists of 12 items for functional capacity, physical status and patient perception of his health and one question for age [70]. In a pilot study, VES-13 accurately identified elderly prostate cancer patients who were defined as having impairment by CGA. The cutoff score of 3 on the VES-13 had 72.7% sensitivity and 85.7% specificity for CGA deficits and was highly predictive for identifying impairment [71, 72], while other investigators challenged these results with a similar design study that failed to show comparable accuracy between the two methods [73, 74].

The *G8 questionnaire* is a very simple screening tool, which includes seven items from the Mini Nutritional Assessment (MNA) questionnaire, while the eighth item is age score (<80, 80-85, >85), for a total score ranging from 0 (poor score) to 17 (good score) [75].

The abbreviated CGA was developed by Overcash *et al.* and comprises a tool of only 15 items [76]. These 15 items include three questions about ADLs; four questions about IADLs; four questions from the Mini Mental State Examination (MMSE) questionnaire; and four questions from the Geriatric Depression Scale questionnaire.

Finally, Hurria *et al.* developed a brief, self-administered cancer-specific tool which assesses the following domains: functional status, comorbidity, cognition, psychological status, social functioning and support, and nutritional status [77].

THE VALUE OF CGA IN ONCOLOGY

Emerging data in oncology practice demonstrate that CGA can improve the clinical management of elderly cancer patients. One aspect of such a thorough assessment is the detection of unknown health problems that may interfere with treatment [78, 79]. An early intervention could reverse some of these problems and help improve treatment tolerance, quality of life and overall survival.

A CGA can also assist decision making and balance the potential treatment benefit against the likely life expectancy as estimated on the basis of functional status, comorbidity and presence of geriatric syndromes [24, 80-84]. Various domains of the CGA have been proven particularly important in geriatric oncology.

Functional status assessment, especially IADL, can predict survival, chemotherapy toxicity, postoperative morbidity, and mortality as it has been demonstrated from studies of CGA in older cancer patients [20, 22, 23, 85].

Comorbidity is also predictive of both treatment tolerance [86, 87] and survival [86, 88] although the latter was not shown in other studies [22, 89, 90], perhaps as a result of the limitations of the instruments used to measure comorbidity [29].

Depression can also be associated with inferior outcomes in older patients with cancer, as it was shown in large population-based [91] and randomized trials [22, 23].

The nutrition assessment is also important since malnutrition is correlated with higher toxicity and adverse outcome in cancer patients [40, 41].

This data suggests that investigators should develop and use a standardized CGA into studies including a high proportion of older patients and test the impact of CGA and of geriatric variables in decision making, in order to improve the outcome of elderly cancer patients. In addition, use of a CGA can stimulate the development of novel endpoints for elderly-specific clinical trials that address quality of survival and functional independence in addition to traditional endpoints of DFS and OS [29].

Moreover, the adoption of a common language by using the validated tools of CGA is essential both for retrospective evaluation of quality of care and for prospective assessment of outcome in clinical trials [10] and is suggested in the guidelines of several organizations [6, 9].

CONCLUSIONS

Though time consuming, CGA is an important tool for initial assessment and intervention, treatment planning and follow-up of elderly cancer patients. The systematic evaluation of physical, emotional and social aspects of patients increases the possibility of identifying underlying conditions that might compromise their quality of life, complicate cancer treatment and deteriorate its prognosis. Currently, only a few clinical studies have incorporated some type of geriatric assessment prospectively. The many different tools

available for measuring the same aspect (comorbidity, depression scales, etc.), the complexity of the complete model of CGA, as well as the lack of established management guidelines according to results, have hampered its use in routine clinical practice. The short screening tools being developed might be user-friendlier and easily applicable in clinical practice. Until we have study results validating some of these shorter tools, comprehensive geriatric assessment remains the gold standard for the evaluation of older cancer patients.

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