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Neurocognitive deficits in older patients with cancer☆

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ABSTRACT

Objective: To assess cognitive function in older adults undergoing cancer care.
Materials and Methods: This is a cross-sectional study, in the University of Texas MD Anderson Cancer Center, in older adults undergoing cancer care. Comprehensive geriatric assessments were conducted prior to surgery, chemotherapy or allogeneic stem cell transplantation, at the Program for Healthy Aging from January 1, 2013 through March 31, 2015. Cognitive assessment was conducted through personal and family interview, and the Montreal cognitive assessment (MoCA). Functional, physical, nutritional, social support, comorbidity assessment and medication review were conducted. Analysis: Patients with mild cognitive impairment (MCI) or dementia were compared to patients who were cognitively intact.
Results: One hundred and ninety-two patients underwent geriatric assessment, mean (±SD) age was 78 ± 7 years, 121 (63%) had some degree of neurocognitive deficit, with 64 patients (33%) presenting with major neurocognitive deficit (dementia), and 57 cases (30%), minor neurocognitive deficit (MCI). Early stage dementia was evident in 50% of cases, moderate stage in 32%, and severe stage in 18%. The prevalence of dementia and MCI were higher than in the general population studies (70–79 years). Associated factors for neurocognitive deficits as compared to older patients with cancer with normal cognition, included a higher comorbidity index ($p = 0.04$), stroke ($p = 0.03$), metastatic disease ($p = 0.04$), and warfarin use ($p = 0.03$).
Conclusion: Neurocognitive deficits (MCI and dementia) are more common in older adults with cancer. Factors associated with neurocognitive deficits include high comorbidity, stroke, warfarin use and metastatic cancer. Identification and management of these conditions is of great relevance in the course of cancer therapy.

1. Introduction

Cancer is a disease associated with aging, and the increasing number of older adults is resulting in a rise in cancer incidence. It is estimated that by 2030 close to 70% of cancer patients will be 65 years of age and older [1]. Age-related diseases such as cognitive impairment and dementia, osteoporosis, diabetes, frailty, and sarcopenia, make the management of older patients with cancer more challenging. It is likely that the effect of chemotherapy on cognitive processes will be superimposed on age-related mild cognitive impairment (MCI) and dementia. Dementia is a general term for a "gradual decline in cognitive capacity severe enough to interfere with daily life" [2]. The prevalence of dementia increases with age, from 5.0% of those aged 71–79 years to 37.4% of those aged 90 and older [3]. It has been reported however, that primary care clinicians may not recognize cognitive impairment during routine history and physical examination, missing the diagnosis in as many as 76% of patients with dementia or probable dementia [4]. Furthermore, the diagnosis of dementia may not occur until patients are in the moderate to severe stages of the disease [4]. Early identification of cognitive

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impairment could allow patients and their families to receive care at an earlier stage in the disease process, improving prognosis and decreasing morbidity. Although current dementia medications cannot alter the course of the disease, the early diagnosis of dementia has been proposed to include health, psychological, and social benefits [5]. The Consortium on Aging Research conference highlighted gaps in cognitive research particularly that there are few studies focused on chemotherapy induced cognitive impairment, and there is insufficient knowledge of the mechanism in chemotherapy induced cognitive impairment [6].

Geriatricians will often treat older adults undergoing cancer care, and will encounter patients at higher risk of neurocognitive deficits. The National Institute of Aging and the Alzheimer Association have established diagnostic criteria for the diagnosis of dementia [7]. The definition of dementia includes cognitive decline which interferes with normal life. Diagnostic criteria for dementia must therefore, include an abnormal cognitive screen such as the Montreal cognitive assessment (MoCA) in addition to functional deficits. Functional deficits are manifested as the loss of 2 or more instrumental activities of daily living -IADLs. These IADLs include medication administration, financial management, arranging for transportation, using the telephone and shopping [7]. Furthermore, it is known that dementia may be preceded by a subclinical phase progressing from normal cognition, to MCI before becoming dementia [8]. (Table 1). Etiologies of dementia are varied, with the most common dementias being Alzheimer's disease (50–60%), vascular dementia (35–40%), diffuse Lewy Body disease (15–20%), and Parkinson's disease dementia in (1–2%). Population studies show that the percentages of people with all dementias are 17% for ages 71–79 years and 34% for octogenarians [9]. Depression is more common in cancer patients, and is considered a risk factor for the development of neurocognitive deficits (NCDs) [10].

Superimposed to the age-related cognitive impairment, are the neurologic changes associated with cancer therapy or what has been called "chemotherapy induced cognitive impairment or "chemo brain" [11]. Standard chemotherapeutic agents, given in clinical dosages, are more toxic to central nervous system (CNS) progenitor cells and oligodendrocytes than they are to cancer cell lines, causing both decreased cell division and cell death [12]. CNS irradiation and chemotherapy can cause severe neurotoxicity leading to cognitive decline and leukoencephalopathy [13]. In cross-sectional studies evaluating cognition in cancer patients, deficits in attention, selective attention, verbal memory, immediate and delayed recall have been documented Current findings suggest that attention and memory impairments might be linked to both frontal and medial temporal lobe dysfunction [14]. Other proposed mechanisms for neurotoxicity include; direct neurotoxic effects of chemotherapy, oxidative damage, immune dysregulation, microemboli, and genetic predisposition [15].

More recently, the term neurocognitive deficits (NCDs) has been proposed with major neurocognitive deficits describing dementia, and minor neurocognitive deficit reflecting MCI (Diagnostic Statistical Manual 5 [DSM 5]). We sought to assess the prevalence of NCDs from the United States population in patients with solid tumors and with hematologic malignancies as compared to population estimates (70–79 years) [9]. We evaluated associated factors for neurocognitive deficits (NCDs) by comparing patients with NCD with patients with normal cognition, seen at the Program for Healthy Aging at MD Anderson Cancer Center.

2. Methods

This was a single site cross-sectional study of older adults with solid tumors prior to surgery or chemotherapy, and hematologic malignancies candidates for allogeneic stem cell transplantation in the rapid recovery program, conducted from January 1, 2013 through March 31, 2015. The research protocol was approved by the institutional review board. The Program for Healthy Aging at MD Anderson was founded in 2013 as a resource for oncologists for specialty care in Geriatric Medicine. Patients were referred to the program for risk stratification prior to initiation of cancer therapy, or in the case of hematologic malignancies, candidates for allogeneic stem cell transplantation. Staffed by geriatricians, comprehensive geriatric assessment (CGA) was performed in all patients referred to the program. Approximately 38% of patient had a personal history of cancer, and were seen for cancer recurrence or a second cancer.

Comprehensive geriatric assessment (CGA) was conducted, utilized for functional status, activities of daily living (ADLs) [16], and the independent activities of daily living (IADLs) [17]. Mood screening and social assessment were conducted using the patient health questionnaire-9 (PHQ-9) [18], and the Medical outcomes study (MOS) scale [19]. For mobility, nutrition, and comorbidity we used the short physical performance battery [20], the mini nutritional assessment [21] and the Charlson comorbidity index [22]. Medication review was carried out. The evaluation for reversible factors of cognitive impairment included computerized tomography (CT) of the brain, thyroid testing, syphilis serology, Vitamin B12, methylmalonic acid, and homocysteine [23]. Specific interventions were implemented for any identified abnormality.

Cognition was assessed by a geriatrician using the MoCA version 3 (MoCA), a normal score is >26 for a white high school graduate. For individuals with lower education, 5 years of school or less, the MOCA basic test is available [24]. The MoCA test has been found to have appropriate validity as compared to neuropsychologic testing [25], and is valid for the assessment of Alzheimer's disease, vascular dementias and MCI [25–27]. The MoCA is considered equivalent or superior to the Folstein MMSE particularly in detecting MCI [28,29]. Patients and their families were interviewed regarding risk factors for dementia such as family history, prior concussion, alcohol or substance abuse, hypertension, hyperlipidemia, diabetes, and long term depression [30,31]. Ethnicity, level of education, cognitive scores, history, and IADLs/ADLs were considered for the diagnosis of neurocognitive deficits. The change in nomenclature from dementia and MCI to major and minor neurocognitive deficit was motivated by the perceived stigma associated with the term dementia [32].

Individuals with MCI had subjective memory loss, an abnormal MoCA score (<26) plus independence in IADLs, or dependence in no more than one IADL. Major neurocognitive deficit (dementia) is defined by the development of multiple cognitive deficits such as verbal fluency, calculation, executive function, visuospatial orientation, abstraction,

Table 1
Cognitive impairment in older cancer patients.

	Criteria for diagnosis		
	Oncology	National Institute of Aging	DSM V
Abnormal MoCA	Cognitive impairment		
Abnormal MoCA + loss of ≤ one IADL		Mild cognitive impairment (MCI)	Minor neurocognitive deficit
Abnormal MoCA + loss of 2 or more IADLs[a]		Dementia	Major neurocognitive deficit

MoCa = Montreal cognitive assessment, IADL = independent activity of daily living, DSM = diagnostic and statistical manual of mental disorders version V, abnormal MoCA ≤ 26. Folstein mini mental state exam (MMSE) has also been used in the literature.

[a] Deficits in 2 or more IADLs such as financial management, medication administration, using the telephone, arranging for transportation and shopping.

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