Neurocognitive deficits in older patients with cancer

Beatrice J. Edwards i,e, Xiaotao Zhang a, Ming Sun a, Holly M. Holmes b, Leena Ketonen c, Nandita Guha c, Peter Khalil a, Juhee Song c, Shelli Kesler e, Jay B. Shah i, Debasish Tripathy f, Vicente Valero g, Richard E. Champlin h

i Department of General Internal Medicine, University of Texas MD Anderson Cancer Center, United States
j Division of Geriatric and Palliative Medicine, UTHealth McGovern Medical School, United States
k Department of Diagnostic Radiology, University of Texas MD Anderson Cancer Center, United States
l Department of Biostatistics, University of Texas MD Anderson Cancer Center, United States
m Department of Neuro-Oncology, University of Texas MD Anderson Cancer Center, United States
n Department of Breast Medical Oncology, Division of Cancer Medicine, University of Texas MD Anderson Cancer Center, United States
o Department of Urology, University of Texas MD Anderson Cancer Center, United States
p Department of Stem Cell Transplantation, University of Texas MD Anderson Cancer Center, United States
q Central Texas Veterans Healthcare System, 1901 Veterans Memorial Drive, mail code 18, Temple, TX 76504, United States

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.

© 2018 Published by Elsevier Ltd.

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 impairment and dementia and their impact on the patient’s quality of life, and functional status are essential for the well being of older adults with cancer.
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

<table>
<thead>
<tr>
<th>Criteria for diagnosis</th>
<th>Oncology</th>
<th>National Institute of Aging</th>
<th>DSM V</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abnormal MoCA</td>
<td>Cognitive impairment</td>
<td>Mild cognitive impairment (MCI)</td>
<td>Minor neurocognitive deficit</td>
</tr>
<tr>
<td>Abnormal MoCA + loss of ≤ one IADL</td>
<td>Dementia</td>
<td>Major neurocognitive deficit</td>
<td></td>
</tr>
<tr>
<td>Abnormal MoCA + loss of ≥ 2 IADLs</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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.

Please cite this article as: Edwards BJ, et al, Neurocognitive deficits in older patients with cancer, J Geriatr Oncol (2018), https://doi.org/10.1016/j.jgo.2018.02.010

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]. Specifc 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 neuropsychological 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,
Among others, and deficits in two or more IADLs. The threshold of 26 on the MoCA may be as low as 20 for ethnic minorities [29,33,34].

MoCA was developed in Quebec Canada among a white population with 13.3 ± 3.4 years of education [35,36]. We used MoCA scores for MCI of 19–24 or early stage dementia 19–23. Further specifics regarding stages of dementia are presented in Supplement 1. It is important to realize that scores may be lower in ethnic minorities (threshold of 20), as has been seen in recent studies [29,33,34]. Imaging included a CT of the brain. Standardized neuropsychological testing should be performed in cases when the routine history and mental status examination cannot provide a confident diagnosis [7]. Similarities between the NIA and DSM5 criteria are seen in Table 1. Steps in diagnosing neurocognitive deficits (NCDs) are seen in Fig. 1.

2.1. Analysis

Descriptive statistics were used to summarize data. Patients with MCI or dementia were compared with patients who were cognitively intact in demographics and comorbidities. Two sample t-test or Wilcoxon rank-sum test was used for the comparison in numeric variables and Chi-square test or Fisher’s exact test was used for the comparison in categorical variables. A p-value of <0.05 indicated a statistical significance. SAS 9.4 (SAS Institute INC, Cary, NC) was used for data analysis [37].

3. Results

We evaluated 192 older adults (130 with solid tumors and 62 with hematologic malignancies). The mean (±SD) age at time of geriatric assessment (GA) was 76 (±6) years, with 94 male patients (49%). Most common cancers were breast cancer 26 (14%), and gastrointestinal 22 (12%), urologic cancers 33 (17%), followed by lung cancer 16 (8%), remaining cases were divided among skin, endocrine, and neurologic cancers. Hematologic diagnoses included acute myeloid leukemia 20 (10%), lymphomas 18 (9%), multiple myeloma 14 (7%). Other diagnosis included myelodysplastic syndrome and myelofibrosis. Individuals were community-dwelling and ambulatory. Older adults, candidates for allogeneic SCT underwent geriatric assessment as part of the rapid recovery program. Approximately 38% of patients presented with a second cancer or a recurrence of original cancer. Past and current cancer therapy is listed in Table 2.

Neurocognitive deficits were present in 121 (63%) cases. The prevalence of major neurocognitive deficit (33%) (dementia) and minor neurocognitive deficit (MCI) (30%) were higher compared to the national level (17% and 6% for age 70–79 years) [9,38,39]. Neurocognitive deficits affected both genders equally. Specifics for determining the stages of dementia are detailed in Supplement 1. In 19 cases (10%) uncertainty about the diagnosis motivated neuropsychological testing that confirmed our presumed findings (early or moderate stage dementia). Associated factors with neurocognitive deficits were evaluated and univariate analysis revealed that these included a higher comorbidity index (p = 0.04), stroke (p = 0.03), metastatic cancer (p = 0.04), and warfarin use (p = 0.03), Table 3. In the majority of cases of NCDs, family reported the duration of cognitive and functional deficits to be over 18 months. Brain imaging reports described cortical atrophy, subcortical ischemic infarcts, and dilatation of sulci and ventricles. Cortical strokes and post-surgical changes as encephalomalacia were also reported. Imaging was negative for brain metastasis. We adjusted for level of education and ethnicity with thresholds of 20 for ethnic minorities as seen in Supplement 1, we did not see patients with <5 years of education.

4. Discussion

We identified an elevated prevalence of neurocognitive deficits – MCI and dementia – in older adults with solid tumors and hematologic malignancies in the United States as compared to population based studies. These findings will have important clinical implications. Our findings contribute to addressing the gap of lack of prevalence studies on chemotherapy induced cognitive impairment among older patients with cancer. Most commonly employed in the oncology literature is the term cognitive impairment, however, such designation does not allow the classification into severity of cognitive impairment. In this study, we highlight that the diagnosis of neurocognitive deficits has to take into account the functional status through the performance on IADLs, and that the cognitive testing threshold may be different in ethnic minorities or those with limited education. Associated factors for neurocognitive deficits included a higher comorbidity, prior strokes, metastatic cancer, and warfarin use. Comorbidities are associated with the development of neurocognitive deficits in a dose response fashion [40,41]. We consider that strokes and warfarin reflect the relevance of the vascular component in NCDs. Metastatic disease is associated with greater neurocognitive deficits, supported by the comorbidity hypothesis as noted above, although it is probable that such patients have received a higher proportion of chemotherapy with consequent effects on neurocognitive function. NCDs affect both genders.
equally in older patients with cancer, in contrast to the female preponderance seen in national studies [9].

Mechanisms underlying aging-related cognitive decline overlap significantly with those believed to be involved in cancer-related cognitive decline. These include DNA damage, chronic inflammation, mitochondrial dysfunction and oxidative stress, among others [42]. Additionally, similar to what is observed in age-related neurocognitive decline. These include DNA damage, chronic inflammation, Alzheimer's disease (HR 1.65) and vascular dementia (HR 2.52) [56]. The identification of cognitive and functional deficits is beneficial on multiple levels. First, a higher prevalence of neurocognitive deficits in older patients with cancer is evident. This raises the need to enhance counseling and education to patients and families, providing them with written instructions and reminders in an effort to improve adherence. Furthermore, the identification of NCDs will allow for the geriatric and oncology teams the opportunity to develop a comprehensive management strategy to enhance medication adherence, avoid clinical complications and provide adequate supervision upon hospital discharge. Second, it assists in determining decisional capacity, an important element in informed decision making. More commonly, individuals with moderate stage dementia may lack decisional capacity and will require the assistance of a power of attorney for healthcare or next of kin [57]. Although it is not the oncologist’s responsibility to diagnose dementia, it is necessary to recognize the lack of decisional capacity when treatment decisions involve assumptions of variable risk to benefit. The National Comprehensive Cancer Network older adult guidelines recommend cognitive assessment when patients appear impaired, fail a short cognitive screen (such as the Mini Cog) or family express concern about memory loss [58,59]. Cancer patients with previously diagnosed dementia receive less cancer treatment [60]. However, many patients with early stage dementia may not appear to be impaired. Thus, identifying the severity of neurocognitive deficits will allow for personalized care. Third, individuals with NCDs are at risk for development of delirium. Targeted preventive interventions [61] would include avoidance of adverse medications, [62] orientation, pain control and early mobilization of patients. Avoidance of prolonged delirium is crucial, as untreated prolonged delirium will lead to the development of neurocognitive deficits [63]. Families should be encouraged to assist the patient with non-pharmacologic interventions such as reorientation and identification of pain. Finally, pre-existing dementia may affect survival in older patients with cancer, as dementia has been associated with an approximate four-fold increased mortality from non-cancer causes [64]. It would appear that the prevalence of mild cognitive impairment and dementia in older patients with cancer may be underestimated [65].

Older adults will sustain cognitive and functional decline with hospitalizations [66], therefore preventive strategies to prevent such declines may be particularly advantageous in this group of patients with NCDs [67]. Individuals with neurocognitive deficits will often require assistance with coordination of care, transportation, and medication administration, particularly in those with multiple comorbidities where medication regimens may become increasingly complex. Although...
those with early stage dementia may have a relatively high level of function, it is important that the care plan be comprehensive, ensuring the availability of a caregiver for those in need of supervision in the period of convalescence.

The prevalence of neurocognitive deficits we identified was higher than that seen in the ADAM and the National Health and Aging Trends Study [68,69]. We postulate that the elevated prevalence of neurocognitive deficits may be due to the superimposed effect of chemotherapy induced cognitive changes on aging related condition such as MCI or dementia. Our study was limited due to selection bias, as typically seen in cross-sectional studies, a small sample size and being a single site study. Patients were referred for geriatric consultation as baseline assessment or pre-intervention assessment, but follow up was challenging. We cannot extrapolate that a similar prevalence of neurocognitive deficits will be seen across all older patients with cancer. Cognitive assessment scales such as the MoCA or Folstein Mini mental exam have been validated in older adults but not specifically in older cancer populations [25–27,70]. Further research in this area is of vital importance, including prospective studies, especially assessing the extent to which neurocognitive deficits impact clinical outcomes.

5. Conclusion

Neurocognitive deficits were more commonly identified in older adults with cancer than in the general population. Associated factors for neurocognitive deficits include higher comorbidity index, stroke, metastatic disease, and warfarin use. Awareness of the extent of cognitive and functional impairment will allow oncologists and geriatricians to develop comprehensive plans of care. Going forward, prospective studies are essential.

Acknowledgement

This research was supported by University of Texas, MD Anderson Cancer Center.

Disclosures and Conflict of Interest Statements

All listed authors are qualified for authorship and no conflict of interest, financial or other, exists.

Author Contributions

Each author has participated and contributed sufficiently to take public responsibility for appropriate portions of the content. Dr. Beatrice J. Edwards has substantial contributions to the obtaining funding, study conception and design; the acquisition, analysis, and interpretation of the data; Mr. Xiaotao Zhang has substantial contributions to the acquisition, analysis, and interpretation of the data; Ms. Ming Sun has substantial contributions to the acquisition, analysis, and interpretation of the data; Dr. Molly Holmes has substantial contributions to the acquisition, interpretation of the data; Dr. Snadita Guha has substantial contributions to the analysis, and interpretation of the data; Dr. Peter Khalil has substantial contributions to the acquisition and interpretation of the data; Dr. Juhee Song has substantial contributions to the analysis, and interpretation of the data; Dr. Vicente Valero has substantial contributions to the interpretation of the data; Dr. Richard E. Champkin has substantial contributions to the interpretation of the data. All authors have participated in the drafting of the article or critical revision for important intellectual content, final approval of the version to be published, and agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the article are appropriately investigated and resolved.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jgo.2018.02.010.

References

[22] Charlson M, Wells MT, Ullman R, King F, Shmukler C. The Charlson comorbidity index can be used prospectively to identify patients who will incur high future costs. Plos One 2014(5):12.e112479.


