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Delirium in elderly patients undergoing chemotherapy for solid cancers and lymphoma

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Abstract

Introduction: *Prevalence and risk factors for delirium in geriatric oncology patients is not well described.*

Aim: *To determine the prevalence and factors associated with delirium in elderly patients undergoing chemotherapy for solid cancers.*

Methods: *We reviewed medical records of patients with cancer aged ≥65 years who were admitted in 2015 with "delirium", "encephalopathy", "confusion", or "altered mental status" within 30 days of chemotherapy for solid cancers and lymphoma. Descriptive and matched pair statistics were used to compare demographics, chemotherapy, medications, comorbidities, and laboratory data between the patients with clinical diagnosis of delirium and their controls matched by age, gender, and cancer diagnosis.*

Results: *One hundred and twenty three patients were hospitalized in an academic comprehensive cancer center. Median (range) age was 71 (65 to 89). 60% were women. Most common cancers (%) were gastrointestinal (25), lymphoma (20), genitourinary (18), pulmonary (15) and breast (12). The most common admissions were for chemotherapy (22%) and infection (21%). 64% were treated with chemotherapy, 24% with chemo and immunotherapy, and 12% with immunotherapy only. A total of 43% received 2 anticancer agents, 32% one, and 18% three agents. Charted delirium prevalence was 7.3% (N=9/123). Five were men. Compared to matched controls, patients in whom delirium was recognized were more likely to have elevated BUNs, acute kidney injury (AKI) and hyponatremia.*

Conclusions: *Delirium was infrequently documented in our cohort of elderly patients admitted for inpatient care following chemotherapy. Elevated BUN, AKI and hyponatremia were significantly associated with the clinical diagnosis and documentation of delirium.*

Keywords: *solid cancer, lymphoma, delirium, chemotherapy, geriatrics*

Introduction

Prevalence of cancer increases with age. Most older cancer patients with good functional status tolerate anti-cancer therapy with limited impact on independence, exacerbation of comorbid conditions, and quality of life [1,2]. Yet, in a UK study, patients with a median age of 72 years did not complete treatment as planned due to toxicity, including delirium. Toxicity occurred in 55.6% patients, although 35% had no greater than grade 2 toxicity [3]. These contrasts exemplify the absence of clear general guidelines for chemotherapy treatment and dosing for the elderly. There are ongoing concerns for the possibility of age related changes affecting the pharmacokinetics and toxicities of medications, including the chemotherapy agents [4-6]. Various cancer treatments can have long-term effects on cognition, which is important for quality of life, adherence to the treatment plan and consenting to treatment [7,8].

Delirium is an acute change in mental status with fluctuating attention and cognition. It occurs abruptly, and is also associated with disorganized thinking and perceptual disturbances [9]. Delirium complicates the hospital course, increases the length of hospital stay and cost per patient, and impairs the quality of life of patients and families [10]. Because delirium has a fluctuating course and hypoactive delirium is less overt, it often remains unrecognized. In hospitalized individuals delirium incidence ranges between 17-30% and has been reported to occur in over half of hospitalized people aged 70 years and older [11,12]. The prevalence of delirium in patients with terminal cancer, who were admitted to a palliative medicine unit was 26%–44%, and 80% in the last days of life and it was a clinical reason for the use of palliative sedation at the end of life [13]. Delirium can be life-threatening and when occurring elderly individuals is often followed by long-lasting irreversible cognitive deficits. Dementia following delirium was diagnosed at a rate of 18.1% per year compared to 5.6% in people without delirium (RR of 3.23) [14]. Recognizing undiagnosed delirium associated with chemotherapy may help us undertake steps to prevent it to avoid its cognitive consequences.

Delirium is most common in males, those over 65 years old, or underlying cognitive impairment, dementia, past delirium, impaired functional status with functional dependence, terminal

illness, multiple medical conditions, infections, electrolyte imbalances and multiple medications. Many medications have the potential to precipitate delirium. Mostly these have centrally activity such as: medications with anticholinergic properties, opioids, benzodiazepines, hypnotics and specific combinations of multiple medications [9]. Conditions that predispose hospitalized individuals to delirium include lung infection (57%), cardiac disease (40%), renal disease (46%), diabetes (31%), and cancer (7%) [11,12].

Inflammatory cytokines such as Il-6, Il2, TNF - alpha, IGF-1 have complex interactions in delirium and in cancer, which are incompletely understood.

We still know little regarding cognitive impairment that occurs immediately after chemotherapy compared to what we know about subsequent long-term cognitive impairment [7]. Prospective delirium studies are challenging to design and can be costly to perform. For this reason we conducted a retrospective chart review to determine the prevalence and factors associated with delirium in cancer patients 65 years or older undergoing palliative or adjuvant chemotherapy or chemo-radiation for solid malignant tumors and lymphoma.

Methods

The study was approved by the Case Western Reserve University Hospital Institutional Review Board.

Subjects included consecutive patients admitted to a major academic comprehensive cancer center for inpatient care following chemotherapy. To be included, patients had to be over the age of 65, diagnosed with solid tumor or lymphoma, and within 30 days of chemotherapy or chemotherapy and radiation during the year of 2015. We excluded those individuals with leukemia, primary central nervous tumors, metastatic to brain tumors and who had undergone surgery within 30 days of chemotherapy to reduce incident delirium attributable to non-chemotherapy causes.

We used the hospital electronic medical record system (EMR) (Allscripts, Chicago, IL) to identify inpatients by ICD 10 codes C00-D49 for "solid cancers", "lymphoma", and G93.40, G93-41, G92.0, 348.31, R41.0 for "delirium", "encephalopathy", "altered mental status."

Subject data from two databases obtained by the IT department and medical records department were matched for eligibility, and the EMR hospitall notes were reviewed by two independent reviewers to build the final database containing subjects for inclusion.

For the study, we defined delirium based on the presence of both: 1) ICD codes for acute cognitive dysfunction "delirium", "encephalopathy", "confusion", "altered mental status" and 2) the occurrence of any of these key words and "agitation" in the written record that included the subject's history and physical exam and progress notes. The diagnosis of delirium used for our chart review mirrored the approach developed in studies validating a delirium diagnosis from hospital records [15-17]. We included various descriptors such as: "confusion, delirium, encephalopathy, altered mental status" and we looked for reports of agitation or disorientation as well as acute onset and associations with acute change in vital signs [15,16]. We arbitrarily selected a 30-day period following chemotherapy for our record review, as delirium is expected to resolve in patients with good functional status within a week or two [18]. Delirium can be prolonged in elderly individuals, but if documented in the clinical record, our approach would still have identified these in the month following chemotherapy. We included chemotherapy-associated delirium for individuals admitted again during our 6-month study window as distinct new episodes of delirium when these admissions were both preceded by chemotherapy or chemo-radiation and followed the prior admission by at least 30 days. Subjects adjudicated to have delirium per study criteria were matched by age, gender and cancer diagnosis to controls from the same sample without delirium.

We recorded demographics, type of chemo- and immunotherapy and potential causative and confounding factors for delirium from the history and physical and progress notes when the individual first met the study criteria for delirium [19]. Confounding factors we considered included: functional status, pre-existing cognitive status, history of delirium or encephalopathy, comorbidities of chronic lung, coronary artery disease, heart failure, cerebrovascular accident and stroke, diabetes mellitus, liver and Chronic Kidney Disease (CKD) ≥ 3. Medications such as opioids, anticholinergics, benzodiazepines, antipsychotics, hypnotics, digitalis, and diuretics. Metabolic and laboratory factors included acute kidney injury (AKI) defined as >30% increase in creatinine compared to baseline, urinary tract infection (UTI), electrolyte abnormalities (serum Na, Mg, blood glucose), hypoxia (SpO2, or ABG if done), hemoglobin, hematocrit, white blood cell count, urine and blood cultures, renal and liver function tests, lactic acid, ammonia, and inflammatory markers (CRP, troponin levels). We also gathered reasons for admission and dates of admission, discharge and delirium onset and resolution if these were specified and recorded.

Statistical analysis

We performed descriptive statistics for the populations overall and delirium presence, and used Chi-square for binomial comparisons and logistic regression analyses to evaluate the associations between the clinical, demographics, laboratory factors and delirium diagnosis as appropriate. McNemar's test, 2-side t -test and nonparametric statistics were performed to identify mean differences and associations for ECOG, demographics, chemotherapy, clinical and laboratory data for the control-matched data. Statistical analysis was performed using a statistical package IBM SPSS Statistics for Windows, Version 19.0. Armonk, NY: IBM Corp. copyright 1989, 2010.

Results

The EMR were reviewed by two reviewers: Y.K. and J.H. We identified 123 individuals who were hospitalized during the period of January 1st to December 31, 2015 after receiving chemotherapy for solid cancers and lymphoma within 30 days of their admission. Demographics and most common reasons for admission are presented in Table 1. Median age was 71 with an interquartile range from 65 to 89 years. Sixty percent were women. Most common cancer types were: gastrointestinal (N=32), followed by lymphoma (N=24), lung (N=18) and breast (N=15). Most common reasons for admission were chemotherapy (N=27) and infection (N=26), of which sepsis was diagnosed in nine and febrile neutropenia in five.

A total of 79 (64.2%) patients had received chemotherapy, 29 (23.6%) chemo- and immunotherapy, and 15 (12.2%) only

Variable	Patients	Percent (%)
Total screened	123	100
Age, Median (interquartile range)	71 (65-89)	NA
Gender, Females	74	60
Cancer type		
Gastrointestinal	32	25
Colorectal	13/32	
Esophageal, Stomach, Hepatobiliary	11-32	
Pancreas	08-32	
Lymphoma	24	20
Genitourinary	22	18
Ovary, Uterine	11-22	
Prostate	05-22	
Renal, Bladder, Testis	06-22	
Lung	18	15
Breast	15	12
Head and Neck	6	5
Other (Peritoneal, Melanoma, Sarcoma)	6	5
Reasons for admission	123	100
Chemotherapy	27	22
Infection	26	21
Pain	16	13
Cardiovascular	7	5
Hematologic complications	7	5
DVT	6	5
Encephalopathy	5	4
Dehydration	5	4
Nausea and vomiting	4	4
Hypoxia	4	4
Shortness of breath	3	2
Other	13	11

Table 1. *Patient demographics and reasons for the hospital admissions.*

Patients	N = 123	100%
Delirium, Encephalopathy	9	7.3
Chemotherapy	79	64
Chemotherapy+ immunotherapy	29	24
Immunotherapy	15	12
Number of anticancer agents		
Single agent	39	32
Combination (2 agents)	53	43
Combination (3 agents)	17	13
Combination (4 agents)	12	10
Combination (5 agents)	2	2

Table 2. *Common chemotherapy regimens for all screened patients.*

immunotherapy. Most of the patients received a combination of two anticancer agents (N=53, 43%), followed by one agent (N=39, 32%), three (N=17, 13%), four and five agents (9%). Sixteen (12%) patients received steroids, five (4%) hormonal and 4% radiation therapy in chemo radiation treatment regimens. Alkylating agents were most commonly used (N=73, 59%), followed by antimicrotubular (N=46, 37%), antimetabolites (N=36, 29%) and topoisomerase II inhibitors (N=26, 21%). Common chemotherapy combinations are in Table 2.

A delirium diagnosis, per study criteria was recorded in 9/123 (7.3%) individuals, five were men. Delirium was the admission reason for five, while four patients developed delirium after initiating chemotherapy during the admission. There were no other subsequent admissions associated with cognitive changes for these patients during the study period.

The delirium patients and their matched controls are compared in Table 3. McNemar and McNemar-Bowker's tests between matched controls for gender, cancer diagnosis and chemotherapy agents were not significant. Only hyponatremia, elevated BUN (Figure 1) and AKI were significantly more prevalent in patients with delirium. There were no statistical differences in chemotherapy, clinical, laboratory results and comorbidities to explain why nine patients developed delirium compared to their matched controls, but there were trends in lower Hct, Hgb, elevated ALT, AST as well as worse ECOG PS and more patients with CAD, CKD stage III, depression, diabetes, and UTI in the delirium group. Only two patients (one from the delirium group) had a documented underlying dementia.

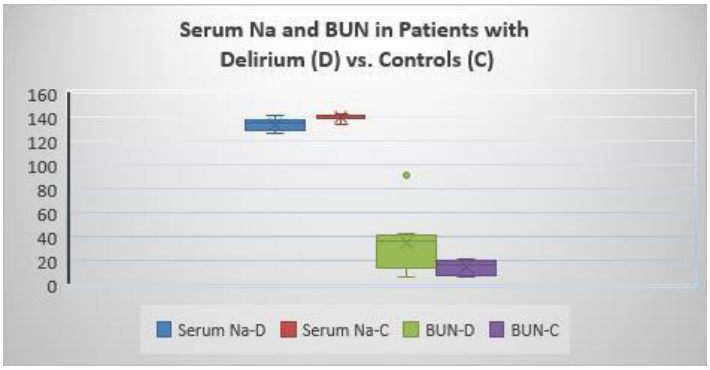

Figure 1. *Comparison between Serum Na and Serum Urea (BUN) in Patients with Delirium (D) and Matched Controls (C).*

Discussion

In contrast to other reports on cancer patients we found low prevalence of delirium (7.3%) documented in patients older than 65 years of age, and hospitalized within 30 days of chemo- or chemo radiation therapy for solid cancers and lymphomas.

We speculate that the low delirium prevalence found in our study might be best explained by underreporting of the cognitive changes if not also due to a selection bias for healthier elderly patients at reduced risk for delirium based that might better tolerate chemotherapy. Due to the retrospective nature of the study we will have missed patients with delirium as our delirium diagnosis was based on documented descriptors of an acute change in cognitive status and the ICD codes of medical diagnosis, which

Age D	Age C	Gender, D and C	Cancer D/C	Admission Cause D	Admission Cause C	Treatment D	Treatment C	Anticancer Therapy D	Anticancer Therapy C
74	71	M	Lymphoma	Sepsis	Bacteremia, Abscess	Ch + I	Ch + I	4 agents	2 agents
69	68	M	Lymphoma	Seizure, Sepsis	Chemotherapy	Ch + I	Ch + I	2 agents	3 agents + corticosteroid
65	66	M	Lymphoma	Encephalopathy, Hyperbilirubinemia	Back pain, L1 spinal mass	Ch + I	Ch	3 agents + corticosteroid	3 agents + corticosteroid
66	73	F	Lymphoma	Encephalopathy	Chemotherapy	Ch + I	Ch + I	4 agents + corticosteroid	2 agents
68	73	F	Lung	Encephalopathy, Fever	Chemo-Radiation therapy	Ch	Ch	2 agents	2 agents
68	67	M	Lung	Dehydration	Hemoptysis	Ch	Ch	2 agents	3 agents
65	67	F	Lung	Encephalopathy	Hypoxia, COPD exacerbation	Ch	Ch	2 agents	2 agents
72	71	M	CUP, Pancreas/ Stomach	Ch	Hypoxia, Respiratory failure	Ch	Ch	3 agents	1 agent
71	70	F	Esophageal, Pancreas/ Pancreas	Hypoglycemia, Anorexia	GI bleed	Ch	Ch	1 agent	1 agent

Table 3. *Demographics and chemotherapy regimen of delirium patients (d) vs. matched controls (c). C: Matched Controls; D: Patients with Delirium; Ch: chemotherapy; I: Immunotherapy.*

did not consistently correlate with the medical documentation. It is possible that some of the patients with cognitive changes after chemotherapy were admitted at other regional hospitals, where we did not have access to these medical records to allow us to identify those episodes of delirium.

Our results differ from the reported delirium incidence of 24% in a retrospective chart review of patients with advanced cancer younger than 65 years old [19]. Despite the similar study methodology, higher delirium incidence can be explained by study population differences - different age groups, advanced cancer, including CNS cancer and hematologic malignancies in the other study compared to ours. In another report of 140 hospitalized patients with a median age of 73 years without CNS cancer involvement (100 studied prospective and 40 retrospectively), 30-60% were diagnosed with delirium [20]. Most prevalent cancer types were lung 20%, gastrointestinal 18%, leukemia 15%, breast 11%. In this study 34% were confused prior to admission, 64% developed delirium during the hospitalization. Higher delirium prevalence compared to our report can again be explained by study population differences – both medical and surgical patients, and one third of individuals had delirium before admission, which will have increased in-hospital delirium incidence. Unlike the previous two studies [19,20] we excluded hematologic malignancies such as leukemia, because these patients are known to develop higher levels of delirium. The prospective follow up in the second report likely contributed to a higher and more adequately captured delirium incidence [20].

Similar to our study only 3% in the retrospective chart review [16] and 8% of patients in the second study [20] who received chemotherapy had delirium. Gastrointestinal cancers were most prevalent in our cohort, but 44% of the patients who had delirium were diagnosed with lymphoma and 33% had lung cancer, which was similar to the higher delirium incidence reported in younger patients with advanced lung cancer [19].

Our results support the previous findings that acute symptom management and infections were the most common reason for hospital admissions in cancer patients among those who develop delirium [19]. Hyponatremia and elevated BUN were significantly associated with delirium in our patients. This is similar to the higher percentage of individuals with delirium reported elsewhere who had elevated BUN 65% and hypo-hypernatremia 60% [20]. Previously reported common causes for delirium were: medications such as opioids (64%), metabolic 53%, infection 46%, recent surgery in 32%, low serum albumin 84%, low total protein 74%; low hemoglobin (Hgb) 74%; abnormal glucose 71% (19,20). We found trends with increased episodes of delirium when patients had a poor performance status ECOG 3, as well as worse anemia and comorbidities such as diabetes, CKD stage III and infection. In a study of 100 consecutive cancer patients with structural predominantly metastatic brain lesions, 36 patients were diagnosed with confusion. Most of the patients (N=57) were diagnosed with a toxic or metabolic encephalopathy [21]. We did exclude patients with brain metastases or brain cancers, and for this reason our delirium incidence was lower, but similar to this study the most common delirium causes in our report were metabolic encephalopathy.

We did not find an association between delirium and chemotherapy or immunotherapy number agents or combinations. Certain chemotherapy drugs for example ifosfamide that cross the blood brain barrier can induce hyperactive delirium [22-24]. Paraneoplastic CNS syndromes such as: limbic encephalitis, cerebellitis have been described in SCLC, thymoma, breast cancer and were associated with chemotherapy [25]. We had only one

patient treated with ifosfamide and one with interleukin-2, but neither patient was in the delirium group. Chemotherapy induced vs. paraneoplastic encephalopathy was suspected in only one patient with lung cancer from our delirium study group, whose encephalopathy did not improve after excluding and correcting all possible metabolic and infectious changes. Our study population is different from patients undergoing bone marrow transplants (BMT), who are well known to have higher levels of delirium post chemotherapy, which is attributed to high doses of ablative chemotherapy, and their cognitive and behavioral disturbances can be long lasting. We were unable to determine if there were alterations in standard chemotherapy regimens due to patient frailty as this was not the main goal of the study, but future prospective studies should correlate doses with neurocognitive toxicity as well.

Our small number of matched control pairs (9 in each group) left us underpowered to establish a statistically significant difference between the two groups. Despite all the limitations of a pilot single center retrospective study, our study is among the few to look into associations between chemotherapy, metabolic abnormalities, infections and acute cognitive changes in patients 65 years or older. Similar to previous reports our findings suggest that delirium causes are predominantly metabolic and likely not so much associated with the chemotherapy agents. Hyponatremia and elevated BUN can be included in models to prospectively identify elderly people, who are at higher risk for delirium post chemotherapy as they appear consistently in reports on delirium in patients with cancer. A challenge to our study was that the medical documentation focused on the cancer treatment and the management of the physical and metabolic complications and less so on diagnosing and managing the cognitive changes. Delirium has an acute onset and fluctuating course, which is potentially reversible when the main physical cause is treated, but when undiagnosed it increases morbidity, the length of hospitalization and negatively impacts the quality of life [10,19]. Our understanding of chemotherapy tolerability in older patients with cancer will improve by consistently applying a comprehensive geriatric assessment. Cognitive assessment is a substantial part of defining frailty [26,27]. Unlike geriatricians and psychiatrists other physicians are inadequately trained to diagnose delirium and mild cases might be missed. The physical and cognitive status of patients is always evaluated prior to chemotherapy but mild hypoactive delirium may go unnoticed.

Conclusion

Our retrospective study found <10% prevalence of delirium in 65 or older cancer patients, who were admitted to a hospital within thirty days of chemotherapy or chemo-radiation for solid cancers and lymphomas. Most likely this was caused by inadequate diagnosis or underreporting of the acute cognitive changes in these patients if not also patient selection. There was no association of the delirium diagnosis and the chemotherapy agents. Delirium predominantly could be attributed to metabolic changes. Elevated BUN, AKI and hyponatremia were significantly associated with delirium and possibly can be included in predictive models to identify elderly patients with cancer, who are at high risk to develop delirium post chemotherapy. Future prospective studies, which control for chemotherapy agents, doses and biomarkers such as Interleukins, IGF, and chemotherapy versus immunotherapy will also increase our knowledge in inflammation and acute and long lasting cognitive change associated with chemotherapy.t

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