Cognitive Effects of Cancer Systemic Therapy: Implications for the Care of Older Patients and Survivors

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ABSTRACT

The number of patients with cancer who are age 65 years or older (hereinafter “older”) is increasing dramatically. One obvious aspect of cancer care for this group is that they are experiencing age-related changes in multiple organ systems, including the brain, which complicates decisions about systemic therapy and assessments of survivorship outcomes. There is a consistent body of evidence from studies that use neuropsychological testing and neuroimaging that supports the existence of impairment following systemic therapy in selected cognitive domains among some older patients with cancer. Impairment in one or more cognitive domains could have important effects in the daily lives of older patients. However, an imperfect understanding of the precise biologic mechanisms underlying cognitive impairment after systemic treatment precludes development of validated methods for predicting which older patients are at risk. From what is known, risks may include lifestyle factors such as smoking, genetic predisposition, and specific comorbidities such as diabetes and cardiovascular disease. Risk also interacts with physiologic and cognitive reserve, because even at the same chronological age and with the same number of illnesses, older patients vary from having high reserve (ie, biologically younger than their age) to being frail (biologically older than their age). Surveillance for the presence of cognitive impairment is also an important component of long-term survivorship care with older patients. Increasing the workforce of cancer care providers who have geriatrics training or who are working within multidisciplinary teams that have this type of expertise would be one avenue toward integrating assessment of the cognitive effects of cancer systemic therapy into routine clinical practice.

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INTRODUCTION

Cancer is largely a disease of older age,¹ and the absolute number of patients with cancer who are age 65 years or older (hereinafter “older”) will increase dramatically over the coming decades with the graying of America.² Unfortunately, this demographic imperative is coupled with a workforce shortage of cancer providers who have geriatrics training or who are working within multidisciplinary teams that have this expertise.³⁻⁵ Consequently some oncologists feel ill prepared to address the complex and unique treatment and survivorship issues of their older patients.⁶

The most distinctive aspect of cancer care of older patients is that they are experiencing age-related changes in multiple organ systems, including the brain, which complicates decisions about systemic therapy and assessments of post-treatment functional outcomes. One age-related change that is often cited as a particular concern of older patients and survivors is cognitive impairment.^{7,8} Therefore, oncology care providers will need to be familiar with

the risks for adverse cognitive effects of cancer when prescribing systemic therapy to older patients and be able to screen for symptoms of cognitive impairment when providing care for this age group.

Cancer-related cognitive impairment was first described three decades ago,⁹ and a fairly consistent, albeit not universal, picture of these deficits has evolved.¹⁰⁻¹² This article uses conceptual frameworks of aging to synthesize what is known about cognitive impairment in older patients with cancer, with an emphasis on identification of the subgroups of older individuals at risk for cognitive impairment after systemic therapy. Finally, this review highlights clinical and research implications of the current body of knowledge for the care of the growing population of older patients with cancer.

THEORIES OF AGING AND COGNITIVE IMPAIRMENT

Given the heterogeneity in health observed across older patients of the same ages, the risks for cognitive impairment after cancer systemic therapy can best

be understood through the lens of aging theories. Aging can be considered the net effect of the temporal accumulation of damage to cellular processes and systems, loss of compensatory mechanisms (ie, diminished reserve), and increased vulnerability to disease and death. Closely aligned to this definition is the clinical concept of frailty, which can be considered a phenotype of aging. This phenotype is characterized by diminished reserve and resistance to stressors caused by collective declines across organ systems leading to vulnerability to insult and adverse outcomes, including cognitive impairment.¹³⁻¹⁶ Thus, it is logical that older individuals with low reserve might be more vulnerable to cognitive impairment than those with greater reserve or younger patients after stressors such as cancer therapy.^{10,17}

Aging is also associated with the accumulation of multimorbidities (eg, diabetes, heart disease) that have direct¹⁸ and indirect¹⁹ neurovascular effects on cognition. Thus, older patients with specific multimorbidities may represent a subgroup vulnerable to accelerated aging and cognitive impairment after cancer systemic therapy.

On a molecular level, aging is characterized by cell senescence. Senescence refers to the state of cells that are metabolically active but can no longer replicate. These senescent cells evoke inflammatory responses and accumulate at sites of pathology, including the brain.^{20,21} Senescent cells can also be considered biomarkers of the frailty phenotype²² that place patients with cancer at risk for cognitive impairment. However, the targets for certain cancer treatments negatively affect biologic markers of aging such as senescence. For instance, increases in tumor suppressor mechanisms through the p53 pathway may be effective in treating cancer but are associated with increased cell senescence, which could in turn lead to accelerating aging and increased risk for cognitive impairment.^{20,21}

This framework raises several provocative questions. If cancer therapy has an impact on cognitive function, does the trajectory of cognitive impairment parallel that of normal aging (phase shift hypothesis)? Or is the trajectory of dysfunction accelerated in comparison to normal aging (accelerated aging hypothesis)?¹⁰ As depicted in Figure 1, the phase shift hypothesis postulates that patients with cancer

experience post-treatment decrements in cognitive function compared with their noncancer counterparts, but further age-associated decline over the course of survivorship occurs at the same rate as for individuals without a cancer history.

Alternatively, if cancer and its treatment are actually accelerating the aging process, we would expect the slope of decline in cognitive function to be steeper for patients in active treatment and survivors relative to their noncancer cohorts. These are not mutually exclusive hypotheses in that a subgroup of cancer survivors (perhaps the majority) may demonstrate the phase shift trajectory, whereas another vulnerable group may demonstrate an accelerated aging trajectory.

In addition to examining specific trajectories of aging, systems theories of aging can provide insights regarding cognition and cancer treatment. One of these, the reliability theory of aging, proposes that complex biologic systems have developed a high level of redundancy ("reserve") to support survival.²³ However, highly redundant systems have a high tolerance for the accumulation of damage when alternate pathways exist and repair does not occur. Loss of redundancy is influenced by the initial extent of system redundancy (primarily genetically determined), the systems' repair potential, and factors that increase failure rate and/or repair ability such as poor health care and lifestyle risk factors such as smoking, obesity, limited physical activity, and/or exposure to environmental toxins. Someone with a low failure rate and/or high repair potential will show fewer signs of biologic aging as they age chronologically, whereas someone with a high failure rate and/or low repair potential will age more rapidly, as evidenced by the development of a disease associated with a specific set of system failures or frailty with a patchwork of failures across multiple systems, hence the differences between chronological and biologic (physiologic) age.

The reliability theory is useful for understanding the cognitive effects of cancer and its treatments in older patients because it does not depend on a given treatment affecting a specific biologic pathway.¹⁰ Thus, one patient may be vulnerable to the DNA-damaging effects of a particular chemotherapy regimen, whereas another

Fig 1. Trajectories of cognitive decline based on theories of aging and frailty phenotype. Adapted from Ahles et al.¹⁰

Fig 2. Pre- to post-treatment change in processing speed by treatment, age group, and level of cognitive reserve among patients with breast cancer (assessed by the Wide Range Achievement Test-Reading). (A) Patients with low cognitive reserve, (B) patients with high cognitive reserve. The bar heights represent post-treatment averages pooled over assessments; the error bars represent the standard error of the averages accounting for repeated measurements from the same individuals. Reprinted with permission.^{10,17}

patient may be susceptible to the impact of the hormonal milieu of endocrine treatments.¹⁰

This framework has potential clinical value because it suggests that the trajectories of cognitive decline are dependent on premorbid cognitive and other system reserves. This idea is supported by research by Ahles et al^{10,17} demonstrating that women age 60 to 70 years with low baseline cognitive reserve who underwent chemotherapy had lower performance on tests of processing speed compared with those not receiving chemotherapy, younger patients, and controls (Fig 2). The next section reviews the key evidence on the cognitive effects of cancer systemic therapy in older patients against the backdrop of theories and processes of aging.

EVIDENCE FOR COGNITIVE IMPAIRMENT AFTER SYSTEMIC THERAPY

Neuropsychology Studies

The largest body of evidence about cognitive impairment in older patients with cancer in association with systemic treatments is from studies of women with breast cancer and, to a lesser extent, men with prostate cancer (Table 1). Several studies that have examined cognitive outcomes for older patients or that include older participants with breast cancers have noted objective and subjective cognitive impairment.^{24-26,32} Other studies that include these types of older patients with cancer have yielded less consistent results.³³⁻³⁶ Such inconsistencies may reflect true underlying differences in participant

risk and reserve postulated by theories of aging. Disparate conclusions may also reflect methodologic issues, including small samples of older patients (range, 13 to 50 patients), variations in the type of control group, or differences in the timing of assessment (eg, patients treated in midlife and evaluated at older ages).²⁶

Another cancer commonly seen in older patients—prostate cancer—has also been a focus of investigation. Several studies have examined whether cognitive impairment occurs with administration of androgen deprivation therapy (ADT) to patients with non-metastatic prostate cancer. Evidence on this issue is mixed (Table 1). For example, a cross-sectional study found higher rates of cognitive impairment in patients with prostate cancer receiving ADT for an average of 23 months compared with age- and education-matched noncancer controls.³¹ In contrast, a longitudinal study in which patients with prostate cancer who were starting ADT were assessed at baseline and observed for 12 months found no consistent evidence of ADT-related cognitive impairment compared with noncancer controls and patients with prostate cancer who did not receive ADT.³⁰ A recent review highlighted these inconsistencies and noted that most studies in this area are characterized by important design weaknesses (eg, small sample sizes and suboptimal control groups) that limit inference.³⁷ However, focusing only on well-controlled studies, it does appear that visual-spatial memory may be impaired with ADT.^{37,38}

Overall, when cognitive impairment is noted in samples with pretreatment or nonexposed cancer or population controls, the

Table 1. Cognitive Effects of Cancer Treatment in Selected Studies That Include Older Patients With Breast and Prostate Cancer

Reference	Participants	Assessment Schedule	Cognitive Domains Assessed	Results
Breast cancer				
Hurria et al ²⁴	Patients older than age 65 years (mean, 71 years; n = 31)	Pre- and postchemotherapy	Attention; verbal and visual memory; and verbal, spatial, psychomotor, and executive function	Declines in visual memory and spatial, attention, and psychomotor function
Hurria et al ²⁵	Patients age 65 years or older (mean, 70 years; n = 50)	Before and after 6 months of chemotherapy	Self-reported learning, working memory, and remote learning	Approximately 50% perceived memory decline; perceived decline related to pretreatment memory
Yamada et al ²⁶	Survivors age 65 years or older (n = 30); age-, education-, and IQ-matched controls (n = 30)	Tested ≥ 10 years post-treatment	IQ, attention, language, visuospatial reasoning, memory, executive function	Survivors had significantly lower divided attention, working memory, and executive function than controls
Ahles et al ¹⁷	Patients exposed to chemotherapy (mean age, 51.7 years; n = 60); patients without chemotherapy (mean age, 56.6 years; n = 72); controls (mean age, 52.9 years; n = 45)	Tested pretreatment and 1, 6, and 18 months post-treatment	Verbal ability, verbal and visual memory, working memory, processing speed, sorting, distractibility, reaction time	Age (older than 60 years) and pretreatment cognitive reserve related to post-treatment processing speed decline in chemotherapy-exposed patients
Schilder et al ²⁷	Patients receiving tamoxifen (mean age, 68.7 years; n = 80) v exemestane (mean age, 68.3 years; n = 99) and controls (mean age, 66.2 years; n = 120)	Tested prior to start and after 1 year of therapy	Verbal memory, visual memory, processing speed, executive function, manual motor speed, verbal fluency, reaction speed, working memory	Tamoxifen associated with lower verbal memory and executive function; women age 65 years or older receiving tamoxifen performed lowest on verbal memory and processing speed
Koppelmans et al ²⁸	CMF chemotherapy (mean age, 64.1 years; n = 196) v noncancer group (mean age, 57.9 years; n = 1,509)	Tested at an average of 21 years post-treatment	Processing speed, verbal learning, memory, word fluency, executive function, visuospatial ability, psychomotor speed	Patients performed worse than controls on learning, memory, processing speed, inhibition, and psychomotor speed
Hurria et al ²⁹	Patients receiving aromatase inhibitors (mean age, 72.4 years; n = 35) and age-matched controls (n = 35)	Tested pretherapy and after 6 months	Verbal function, learning and memory, visual memory, spatial, psychomotor, attention, and executive function	No significant cognitive decline but PET scan showed brain metabolic changes at 6 months
Prostate cancer				
Alibhai et al ³⁰	Patients receiving ADT (mean age, 69.3 years; n = 77) matched to non-ADT cancer controls (n = 82) and noncancer controls (n = 82) by age and education	Tested before and at 6 and 12 months after ADT	Attention, processing speed, verbal memory, verbal fluency, cognitive flexibility, immediate memory, working memory, visuospatial ability	No patient-control differences at 6 months, but significantly less improvement in ADT patients for some tests within attention, visuospatial, and executive domains at 12 months
Jim et al ³¹	Patients receiving ADT (mean age, 69 years; n = 48) matched to noncancer controls (n = 48) by age and education	Tested at one time point during treatment	Verbal memory, verbal fluency, visual memory, visuospatial function, executive function	Patients did not differ from controls on any specific domain but had a higher rate of overall cognitive impairment

Abbreviations: ADT, androgen deprivation therapy; CMF, cyclophosphamide, methotrexate, and fluorouracil; PET, positron emission tomography.

most commonly affected domains include verbal working memory, visual memory and visual-spatial domains, executive function, and/or processing speed (Table 1).^{11,39-44} These cognitive impairments have been observed after considering surgery type, anxiety, depression, and/or fatigue, and they persist for variable periods of time from 1³⁹ to as many as 10 to 20 years post-treatment.^{28,45,46} Beyond these fairly consistent associations, the link between cancer systemic therapy and cognitive impairment is further supported by observed dose-response relationships, with greater exposure in terms of dose or treatment duration leading to higher rates of cognitive impairment.¹²

As summarized in Table 2, impairment in one or more domains of cognitive function could have important effects on the daily lives of older patients and survivors, including difficulty tracking medications and following medical advice, difficulty coordinating care across multiple providers, difficulty with tasks such as bill payment and meal preparation, need for additional time to perform these types of tasks, and social isolation to conceal deficits.¹² Thus, it will be important to increase our research on cancer and cognition in the older population, because this is the group most likely to be faced with the simultaneous risks of cancer and the adverse effects of treatment, along with other diseases related to brain aging.^{5,47-49} Expansion of studies of cognition

Table 2. Domains of Cognitive Function Affected by Cancer Systemic Therapy and Implications for Function in Older Patients With Cancer

Domain	Brain Region	Impact on Function
Working memory	Bilateral prefrontal and parietal regions	Ability to organize activities, arrive on time, make plans and decisions, correct errors, conceptualize problems, react with appropriate speed
Executive function	Ipsilateral dorsal lateral prefrontal cortex	
Psychomotor speed	Distributed frontal subcortical network; bilateral frontal and pyramidal and extrapyramidal motor systems	
Attention, concentration	Distributed frontal subcortical network	Ability to pay attention to new information and process the information
Language and verbal memory	Left hemisphere	Ability to fluently bring words to mind
Learning and episodic memory	Medial temporal lobes and prefrontal cortex	Ability to learn or recall new information
Visual memory	Right hemisphere	Ability to integrate visual information with motor activities
Visuospatial	Right parietal and bilateral frontal regions	

from breast and prostate cancer to other common cancers in older populations (eg, colorectal cancer) could also further support clinical care of this age group.

Studies of Structural and Functional Brain Neuroimaging

To the extent that cancer treatments may accelerate or mimic the effects of aging to produce cognitive impairment in domains that impact daily function, one would expect some overlap in the brain structures affected by aging and by cancer treatments. Overall, this has been the case, with similar brain structural alterations seen in aging and cancer-related cognitive impairment, including decreases in overall brain volume, gray matter, white matter connectivity, and hippocampal volume.^{10,28,50-53} For instance, imaging studies have demonstrated that total gray matter volume reliably decreases with advancing age, with regional changes exhibited mainly in the frontal cortex and in regions around the central sulcus, including the hippocampus.⁵⁴ Lower hippocampal volume is related to memory functioning and has been observed in patients with breast cancer after treatment.⁵⁵

Global white matter also diminishes with increasing age.^{54,56} Reduction in volume of frontal brain structures and changes in the integrity of white matter tracts have been reported after breast cancer chemotherapy as have alterations in brain activation on functional neuroimaging.^{50,57-62}

Alterations in brain function have also been observed among patients with breast cancer by using functional MRI (fMRI) and functional positron emission tomography.^{51,63,64} Interestingly, several studies have found patterns of over activation in patients with breast cancer compared with controls both before and after

adjuvant chemotherapy.^{10,57,65,66} These results have been interpreted as evidence of compensatory activation (ie, recruitment of alternate brain structures to maintain performance on neuropsychological testing) and may explain why some patients report cognitive problems but score within the normal range on neuropsychological testing. The findings also suggest that abnormal patterns of activation exist before adjuvant therapy in some patients and may be a predictor of post-treatment cognitive problems. However, most of these latter imaging studies have been among patients younger than age 65 years with breast cancer.

Although there are limited studies in older patients with prostate cancer, one study used fMRI and neuropsychological testing to compare men who received ADT with those who did not.⁶⁷ They noted that after 6 months of treatment, there were no differences in average cognitive function, but men receiving ADT showed impaired brain activation and abnormal functional brain connectivity on fMRI.⁶⁷

It will be important to investigate these brain structural links between aging, cancer therapy, and cognitive impairment related to systemic therapy in larger samples of older patients with cancer, especially in longitudinal settings with a healthy aging control population. At present, the results are consistent with those postulated by theories of aging. Taken together with the correlated neuropsychological testing and neuroimaging results, the body of evidence suggests that the observed cognitive effects of cancer therapy are not an artifact. However, it appears that only a susceptible subgroup of older patients experience cognitive impairment after systemic cancer therapy.^{10,11,17} The next section reviews what is known about factors that might identify those older patients at greatest risk for cognitive impairment after systemic therapy.

RISK FACTORS FOR COGNITIVE IMPAIRMENT FOLLOWING CANCER SYSTEMIC THERAPY

The precise biologic mechanisms and pathways underpinning cognitive impairment after cancer and/or its treatments remain uncertain; therefore, it is difficult to validate risk markers. Common candidate pathways and risk factors are consistent with theories of aging and include those that affect accumulation of damage, repair of damage, and baseline system redundancy. Accordingly, researchers have investigated changes in hormonal milieu, inflammation, oxidative stress, DNA damage and compromised DNA repair, decreased brain blood flow or disruption of the blood-brain barrier, genetic susceptibility, direct neurotoxicity or damage to specific brain regions, decreased telomere length, and cell senescence (Table 3).

Hormonal levels decrease over the life span. In noncancer populations, hormone replacement therapy seems to improve cognition in postmenopausal women.⁹⁵ hormone replacement therapy also appears to decrease the risk of developing Alzheimer's disease by up to 29%,⁹⁶⁻⁹⁸ although this result is not universally noted.⁹⁹⁻¹⁰¹ In patients with cancer, hormonal therapies have been implicated in cognitive impairment after treatment for breast cancer.^{27,72-76} However, effects are not universal and may not be observed with all hormonal therapies. For instance, a recent clinical trial reported cognitive declines in verbal memory and executive function among women treated with tamoxifen but not exemestane.²⁷ This result is biologically plausible because estrogen receptors, the target of tamoxifen and other drugs in its class, are found in large numbers in the frontal lobe and hippocampus⁶⁸⁻⁷¹; these same areas have been noted to have abnormalities on

Table 3. Risk Factors for Cognitive Impairment Following Cancer Systemic Therapy

Category	Mechanism	Source
Hormonal milieu		Bender et al ⁶⁸ Ciocca and Roig ⁶⁹ Shilling et al ⁷⁰ Deroo and Korach ⁷¹
Tamoxifen	Effects on brain estrogen receptors in frontal lobe and hippocampus; maintaining telomere length	Schilder et al ²⁷ Castellon et al ⁷² Jenkins et al ⁷³ Bender et al ⁷⁴ Collins et al ⁷⁵ Schilder et al ⁷⁶ Lee et al ⁷⁷
Aromatase inhibitors	Decreased circulating estrogen	Schilder et al ²⁷ Jenkins et al ⁷³ Bender et al ⁷⁴
Androgen deprivation	Reduced testosterone	Moffat et al ⁷⁸ Thilers et al ⁷⁹
Inflammation/ cytokines and cytokine regulation	Modulation of neuronal and glial cell functioning, neural repair, and the metabolism of neurotransmitters important for normal cognitive function	Wilson et al ⁸⁰ McAfoose et al ⁸¹ Ganz et al ⁸²
Oxidative stress; DNA damage and/or repair	Treatment-induced DNA damage targeted to tumor and brain cell death; decreased brain plasticity and repair	Conroy et al ⁵⁰ Migliore et al ⁸³ Migliore et al ⁸⁴ Ganz et al ⁸⁵
Genetic susceptibility		Ahles et al ⁴⁸ Saykin et al ⁸⁶ McAllister et al ⁸⁷ Egan et al ⁸⁸ Hariri et al ⁸⁹ Pezawas et al ⁹⁰
<i>ApoE</i>	Uptake, transport, and distribution of lipids; role in neuronal repair and plasticity after injury	Ahles et al ⁴⁸
<i>COMT</i>	Metabolism of catecholamines; effects on neurotransmitter levels	Small et al ⁴⁴ Lindenberger et al ⁹¹
<i>BDNF</i>	Neuronal repair and survival, dendritic and axonal growth, signal potentiation	Egan et al ⁸⁸ Hariri et al ⁸⁹ Pezawas et al ⁹⁰
<i>TNF-α-308</i> promoter SNP	Inflammation	Ganz et al ⁸²
Vascular integrity	Variation in blood-brain transporters (eg, multidrug resistance 1 [<i>MDR1</i>] gene coding for protein P-glycoprotein); effects of diabetes or vascular disease; direct toxicity to brain cells and/or cell death and reduced cell division	Ahles et al ⁴⁸
Telomere length	Accelerating aging process and/or direct apoptotic effect on neuronal mitotic cells	Maccormick ⁹²
Cellular senescence	Inflammation and damage	Ahles et al ¹⁰
Stem cells	Neurotoxicity to progenitor cells	Seigers et al ⁹³ Dietrich et al ⁹⁴

NOTE. Adapted.^{47,48}Abbreviations: *TNF-α-308*, tumor necrosis factor-α-308; SNP single nucleotide polymorphism.

imaging studies.^{52,102} One intriguing result of the trial comparing hormonal therapies was a preliminary result that tamoxifen had larger effect sizes and affected a greater number of cognitive domains in women age 65 years or older compared with women younger than age 65 years.²⁷

In contrast, aromatase inhibitors like exemestane block conversion of androgens into estrogens, and studies of their effect on cognition have been inconsistent.^{27,73,74} Hurria et al²⁹ recently compared cognitive performance of older patients with breast cancer treated with an aromatase inhibitor with matched healthy controls in a longitudinal study and found no evidence for cognitive decline on the basis of neuropsychological testing. However, positron emission tomography imaging revealed metabolic changes, primarily in medial temporal lobes in patients compared with controls.

As noted previously for prostate cancer, the main finding from a recent review of studies of men treated with ADT is that spatial memory may be especially affected.³⁷ The putative mechanism for this and other adverse cognitive effects is the decline in testosterone levels produced by ADT. This hypothesis is supported by research showing that naturally occurring reductions in testosterone among healthy men are also associated with cognitive impairment, especially in domains involving visual and spatial abilities.^{78,79} The link between nonverbal abilities and testosterone is further supported by research on sex differences in cognition, which has consistently demonstrated differences in visuospatial ability between the sexes favoring males.¹⁰³

In terms of other risk factors that affect the ability of various systems to repair themselves, Conroy et al⁵⁰ recently conducted an innovative study with breast cancer survivors and matched noncancer controls. The sample population ranged in age from 41 to 79 years old; the patients with cancer were 3 to 10 years post-treatment. They found that oxidative DNA damage was higher in patients than controls and that DNA damage was correlated with lower scores on neuropsychological tests of cognitive function and less frontal gray matter density and brain activation on fMRI. Although only small numbers of patients were assessed ($n = 48$), the result is interesting because oxidative DNA damage and diminished DNA repair mechanisms are also markers of senescence¹⁰⁴ and are seen with mild cognitive impairment in noncancer settings.^{83,84} Hormonal therapies may also be associated with increased DNA damage.¹⁰⁵

Although it is widely held that most systemic chemotherapy agents do not cross the blood-brain barrier in significant doses, data from animal studies suggest that small doses of common chemotherapy agents can cause cell death and reduced cell division in brain structures crucial for cognition, even at doses below those needed to effectively kill cancer cells.⁴⁸ In humans, the amount of systemic agents that enters the brain may be modified by genetic variability in blood-brain barrier transporters.

Other genetic influences may also modulate the influence of exposure to cancer treatment via effects on baseline system redundancy.^{48,87} Polymorphisms of the apolipoprotein E (*ApoE*) and catechol-O-methyltransferase (*COMT*) genes have been studied for associations with cognitive impairment after cancer treatment,^{44,46} and numerous other candidate genes may play a role (eg, brain-derived neurotrophic factor [*BDNF*] and the tumor necrosis factor α 308 [*TNF-α-308*] promoter single nucleotide polymorphism).^{48,82,87-91}

Ahles et al⁴⁶ noted that 10- to 20-year breast cancer survivors who received chemotherapy and were *ApoE* $\epsilon 4$ -positive had greater impairment in the visual-spatial and visual memory domains compared with $\epsilon 4$ -negative survivors receiving this treatment (average age, 56 years), although others have not noted this provocative relationship.⁵³

COMT plays an important role in prefrontal dopamine regulation in the frontal lobes and has been shown to be associated with executive function in normal controls. In a study of cancer and cognition by Small et al,⁴⁴ patients with breast cancer treated with chemotherapy who were *COMT*-valine carriers performed worse on measures of attention compared with *COMT*-methionine homozygotes, although the average age of these women was well below 65 years. Of note, in general populations, Lindenberger et al⁹¹ have found an age interaction with the *COMT* gene.

As the validity of personalized medicine becomes more established, understanding the genetic and other risk profiles of older patients most vulnerable to cognitive decline could be useful in clinical decision making about systemic therapy and risk of cognitive impairment and in identifying survivors in greatest need of intensive surveillance over time.

SUMMARY AND PRACTICE IMPLICATIONS

From the preceding review, it is clear that there is a consistent body of evidence from controlled studies using neuropsychological testing and neuroimaging that supports the existence of cognitive impairment among some older patients with cancer after receiving systemic therapy. However, it is also apparent that there is not yet sufficient evidence to develop clinically useful, validated tools for risk prediction of cognitive impairment related to specific cancer systemic therapies. Moreover, older individuals vary along a continuum of physiologic and cognitive reserve from high (ie, biologically younger than their age) to frail (biologically older than their age). Although the frail phenotype is obvious in clinical practice, the challenge remains to reliably identify those with low reserve in the absence of overt symptomatology so that treatment decisions can be tailored to physiologic rather than chronological age.

One implication for oncology practice of the current body of evidence on cognitive impairment after systemic therapy is that older patients be evaluated for frailty and reserve.¹⁰⁶ Other articles in this issue include in-depth reviews of state-of-the-art recommendations for such assessments. Although still not fully tested for predictive validity or impact on outcomes,¹⁰⁷ many of those assessment tools can be used during routine clinical encounters and could be of help in multidisciplinary team care.

As the field of geriatric oncology moves forward, it will be important to ensure that recommended batteries of tests and biomarkers have high predicative validity for the outcomes of interest, including cognitive impairment. The results of these assessments could then be useful as adjunct tools for identifying subgroups of older patients who are likely to be at highest risk for cognitive decline after systemic therapy.¹⁰⁸ This information could be used together with clinical data

and results of tumor multigene profiles in discussions with patients about balancing benefits and harms of systemic therapy. Consideration of the cognitive impact of systemic therapy could possibly change treatment decisions, especially when indications for systemic therapy are equivocal, because cognitive changes are among the symptoms most feared by older adults.^{7,8} Furthermore, clinicians need to be aware that, with the aging of the population, they will be diagnosing increasing numbers of patients with pre-existing mild cognitive impairment or dementia that may be unrelated to their cancer but can have significant implications for treatment decision making and clinical management.

Surveillance for risks for and presence of cognitive impairment is also an important component of long-term survivorship care, especially with older patients. This is especially important because the time course of impairment following cancer systemic therapy is variable, improving in some patients over time and persisting for up to 20 years in others.^{12,45} The National Comprehensive Cancer Network recently added this dimension to its recommendations for survivorship care.¹⁰⁹ When data become available on effective interventions, such as cognitive training, exercise, and other approaches, these could be integrated into active treatment and survivorship care to prevent or treat cognitive impairment in older patients.¹¹⁰⁻¹¹⁶ Finally, future therapeutic trials of systemic agents could include intermediate end points of relevance to the older age group, including cognitive function and trajectories of frailty.¹¹⁷⁻¹¹⁹

Given the demographic imperative of a rapidly growing older population, increasing cancer incidence with advancing age, and the increasingly chronic nature of the most common cancers, novel research in older patients with cancer and cancer survivors will be critical for developing practice guidelines aimed at minimizing cognitive impairment while maximizing survival outcomes of older patients. Clinicians and their older patients can advance the field by actively encouraging and participating in research designed to improve the care and outcomes of older patients with cancer.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

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