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Neurocognitive Challenges in Brain Tumor Survivors: Is There Anything We Can Do?

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Neurocognitive and neuropsychological deficits after treatment of primary and metastatic tumors in the brain are significant, much feared survivorship challenges for a group of patients that is enlarging as treatment effectiveness for primary brain tumors and metastatic cancers improve. When reporting the initial phase II results[1] that motivated the phase III trial that accompanies this editorial,[2] Shaw et al framed this issue with a quotation from a survivor, Susan Sontag, 16 years after combined-modality therapy: "'Everything I do is slow. I walk, talk, and think slowly… I still have no short-term memory… Much of the time I can't even remember the names of relatives and close friends… I am always confused… Because I look normal and often sound normal, people assume I am normal. But I'm not… I get depressed a lot knowing that I will never have my competence back.' (Sontag Foundation Distinguished Scientists Awards ceremony speech at the Society for Neuro-Oncology Meeting, Toronto, Canada, November 20, 2004.)"[2(p1415)] Have there been advances in the last decade to address this problem, and does the phase III trial now reported provide evidence that contributes to an appropriate strategy?

Patients frequently enter into therapy with baseline deficits that result from direct brain injury by the tumor as well as other unrelated illnesses. The most effective approach to maintaining maximal function involves strategies to prevent further damage to the brain. Although the focus has been on controlling tumor progression, which poses the most immediate threat to function and life, prevention of therapy-related injury to the brain is increasing in importance as survival outcomes improve. Strategies for injury prevention include functional imaging to guide safe surgery,[3] limiting daily radiation fraction size as well as total dose,[4–6] radiotherapy target definition guided by improved imaging,[7] highly conformal radiotherapy administration techniques, and replacement of whole-brain radiotherapy with highly focused stereotactic radiosurgery for many patients with brain metastasis.[8] A recently reported multi-institutional phase II trial[9] suggested that the novel approach of whole-brain radiation with a constrained dose to the hippocampal neural

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progenitor cells, which are important to learning, may yield better neurocognitive outcomes. With the anticipated development of additional systemic agents that cross the blood-brain barrier, attention will be required to evaluate the effects on cognition as well as optimal safe timing in relation to radiotherapy.

The study by Rapp et al[1] that accompanies this editorial investigated a pharmaceutical with the potential to palliate neurocognitive symptoms or perhaps even modify the injury process after the often unavoidable damage has occurred. Donepezil, a selective oral acetylcholinesterase inhibitor that has been approved for use in Alzheimer's disease (AD), increases acetylcholine signaling by slowing its synaptic degradation. Multiple randomized trials in AD confirmed marginal improvement in measures of cognitive function, activities of daily living, caregiver burden, and/or independence.[10–13] Although the mean/median benefits are modest, some patients experience larger benefits or meaningfully delayed progression of disability. Evidence suggests that acetylcholinesterase inhibitors can improve neurocognitive function in other disorders, including vascular dementia,[14] multiple sclerosis,[15] and Parkinson's disease.[16] The appropriate use of this drug in AD and other illnesses provides guidance for its use in the population of patients with brain tumors.

There is mechanistic rationale to support the plausibility of a benefit from acetylcholinesterase inhibition in patients with brain tumors treated with radiotherapy.[17,18] Originally, anticholinesterase drugs were introduced for AD as a means to ameliorate the direct effect of widespread loss of cholinergic fibers on memory function. Animal models[19,20] provide limited evidence that acetylcholine signaling is reduced after radiotherapy as well. However, acetylcholine may have additional relevant effects on the brain injury process itself, beyond a direct role in memory function, and thus could potentially modify the ongoing disease process as well as palliate symptoms.

Hippocampal degeneration is an important feature of AD, and damage to hippocampal neural progenitor cells may also be significant in neurocognitive injury that results from radiotherapy.[7,9,21] There can be a stabilization of hippocampus volume in patients with AD who are treated with donepezil.[22] In rodent models, impairment of cholinergic nuclei, which project to the hippocampus, impairs neurogenesis by decreasing survival of so-called newborn neuronal cells—an effect reversed by donepezil.[23] Therefore, it is of interest that radiotherapy arrests neurogenesis in the hippocampus, although it is unknown whether donepezil would address this injury.

Acetylcholinesterase inhibitors may also influence aspects of the brain microenvironment that are regulated by cholinergic stimulus. Microglial cells, the resident macrophages in the CNS, are activated in inflammatory diseases including AD,[24] as well as in the response to radiotherapy.[25,26] Acetylcholine receptors on the surface of microglia initiate a signaling cascade that inhibits inflammatory responses,[23,24] potentially part of a feedback mechanism that may limit cell death from the neurotoxic environment resulting from chronic inflammatory processes.

There are other mechanisms by which improved cholinergic signaling may improve brain function after therapy. Radiotherapy affects normal tissues via microvascular injury.

Donepezil improves perfusion[27] in patients with AD and is useful as a treatment for microvascular dementia.[14] The effect of acetylcholine on perfusion specifically localizes to areas of the brain that are involved in learning, including right anterior cingulate, dorsolateral prefrontal, and bilateral temporoparietal areas.[14] Finally, it is relevant that a portion of patients with brain tumors who meaningfully benefit from this drug may respond not only as a result of original tumor injury or unrelated brain illness, but also because a favorable effect may occur that is unrelated to pathologic conditions: a randomized research study confirmed that this drug could improve memory function, localizing to the hippocampus, even in a population of young healthy adults (median age, 23 years) confirmed improved memory functions localizing to the hippocampus.

The phase III study reported by Rapp et al[1] was motivated by the results of a single-arm phase II trial[2] of donepezil administered for 6 months (which, like the study by Rapp et al, was also conducted by investigators at Wake Forest) that demonstrated improvement in cognitive function, brain-specific symptoms, and quality of life. Although definitively studying neurocognitive outcome in patients with tumors is challenging, the study by Rapp et al was well designed to confirm whether there was a benefit to the experimental intervention. The patient population was well selected: all patients had completed radiation treatment at least 6 months before (median, 38 months) and were free from disease progression, directing the study toward long-term consequences for brain function without the confounding transient impact of acute or subacute treatment effects, ongoing systemic therapies, or progressive tumors. Appropriately selected, validated neurocognitive tests were used,[29] and compliance was excellent for a study of this type: 75% of patients proceeded through the testing, and more than 90% of the patients were compliant with the drug, whether placebo or donepezil. The results were robust when analyzed with assumptions about lack of efficacy in noncompliant patients being treated with donepezil. Limitations include that the population was heterogeneous with respect to primary and metastatic brain tumor diagnosis, deficits at the time of enrollment, and radiotherapy dose and volume. In addition, information about systemic therapy that could result in transient or permanent cognitive and quality-of-life effects was not available.

Nevertheless, donepezil (10 mg per day) demonstrated a statistically significant benefit for this population with respect to memory, motor speed, and dexterity after 24 weeks of drug administration compared with placebo, but not the primary end point of composite cognitive score.[1] These results are similar to those observed in other neurocognitive diseases treated with cholinesterase inhibitors. Importantly, the benefit was greatest in those with the most significant impairment before the study intervention. Measures of quality of life and function, which would provide information about clinical significance of the observed improvements, have not yet been reported. This study was not powered to provide information relevant to subgroup of patients by diagnosis, use of whole-brain radiotherapy, or other treatment/tumor parameters.

This study should be considered in the context of other ongoing research efforts that are directed at improving cognitive outcome. As discussed, hippocampal-sparing radiotherapy[9] may prevent injury, although with significant cost and effort and the risk of preventable recurrence in the underdosed region. The recently reported randomized trial RTOG

(Radiation Therapy Oncology Group) 0514[30] tested memantine (an N-methyl-D-aspartate glutamate receptor antagonist beneficial for AD) for 6 months with therapy initiated during whole-brain radiotherapy for metastatic cancer. In contrast with the study by Rapp et al,[1] the initiation of therapy during radiation treatment may provide the greatest potential for modifying the process, but also, any benefit may be confounded by acute toxicities, other treatments, and disease progression. Benefits were demonstrated for time to cognitive decline, executive function, processing speed, and delayed recognition at some time points but not for the primary objective of delayed recall. However, the robustness of any conclusions may be questioned, given that only 29% (149 of 508) patients were analyzable; the remainder were excluded as a result of death (34%), withdrawn consent (11%), and noncompliance with testing (26%).

Questions remain about whether this information can now be used to help affected patients at this time, and what important research questions may result in advancements in the near future. As discussed, it is critical to prevent as much therapy-related brain injury as possible. Particular areas of research that may be worthwhile in the near future include development of novel imaging of tumor and functional brain to better guide surgery and radiation, definitive testing of hippocampal-sparing techniques, systemic agents that may delay the need for radiation or substitute for radiation in the treatment of subclinical disease volumes, identification of treatment tolerances of areas of the brain that are important in cognition,[7,26] and further definition of which patients can be suitably treated with smaller, highly conformal or stereotactic targeting of radiotherapy. Radioprotective agents have not been effective thus far, and may also protect the tumor.

Once cognitive deficits that persist after the acute period of therapy have been identified, comprehensive neurocognitive rehabilitation services should be engaged. Although it has been considered self-evident that rehabilitation is helpful, Gehring et al[31] have reported the results of disciplined study of cognitive rehabilitation in patients with glioma. Their randomized trial included 140 long-term glioma survivors[31] (median survival, 5.2 years; 43% treated with radiotherapy) with mild or moderate impairment (Karnofsky performance status > 70). The group randomly assigned to rehabilitation had benefit in attention, verbal memory, and mental fatigue. The program consisted of developing new strategies to use intact cognitive pathways to perform impaired functions in new ways as well as using practice over time to retrain. Evidence suggested that younger patients and those with more years of education experienced greater improvements,[32] in keeping with the brain reserve theory, and emphasizing that continued study is needed to guide the optimization of rehabilitation strategies toward the needs of individual patients. For those with more severe impairments, cognitive deficits themselves may of course limit the potential of many patients to retrain or learn compensatory strategies.

The study reported by Rapp[1] suggests that a pharmaceutical intervention, donepezil, may be helpful for patients experiencing cognitive difficulties, although the average benefit was small and additional data about clinical significance are needed. However, this trial confirms that the drug clearly helps some patients, with the greatest response in the most impaired patients. Given that the drug is generally well tolerated, except for reversible nausea, vomiting, and diarrhea in less than 20% of patients, the results of this study provide

appropriate justification to administer donepezil to affected patients and assess them for an effect over at least several months. Routine or prophylactic use of this drug in patients or continuation without clinical benefit is not sufficiently supported or addressed by these data. Before such use could be recommended, a long-term benefit for patients without significant decline at the time of drug therapy, superior to the benefit of initiating treatment at the time of symptom development, would need to be demonstrated. The cognitive effects of tumor and treatment injury do not inevitably and relentlessly progress,[33] as with AD; in the context of AD, the drug may be continued for some patients who do not actually improve on the basis of evidence of slowing of the expected decline.[34,35]

Drug administration was continued for 6 months in the study by Rapp et al,[1] but on the basis of experience with AD, in which neurocognitive measures of treated cohorts decrease to match those of untreated control patients after drug cessation,[36,37] it is likely that lifelong therapy will be appropriate for responders. Several cholinesterase inhibitors are available, including rivastigmine and galantamine, and patients with AD may respond to an alternate agent even after the initial drug has failed. Optimal dosing for patients with cancer remains to be determined, but trials of dose escalation in AD have not provided clarity of benefit relative to the increased GI adverse effects. Memantine[30] is also an appropriate alternative choice, although the reported trial of memantine in patients with brain tumors included neither patients with primary brain tumors nor longer-term survivors who already had cognitive difficulties. Whether there is a benefit to the combination of memantine along with an acetylcholine esterase inhibitor is uncertain in AD, and requires study in patients with cancer. Ongoing research into novel drug therapies for AD and other dementias may ultimately lead to better choices for patients with brain tumors.

With these steps—prevention of injury, rehabilitation, and use of these drug therapies while monitoring for benefit—there is now reason for cautious optimism that the proportion of patients who find themselves in the challenging situation described by Sontag will begin to grow smaller, even as long-term survival improves. That there is cause for optimism is clear, although the measures available at this time for improving cognitive function are only marginally beneficial for most patients. A barrier to optimal use of any of these interventions is the need for a validated easy-to-use instrument that may be used in routine oncology practice and has sufficient sensitivity to screen for and measure mild to moderate impairments that are specific to this population at risk for both focal injuries and global deficits. For the present, subjective scoring by patients, validated by caregivers, of so-called functional competence may provide a meaningful metric[35] in keeping with the ultimate objective of improved patient and caregiver satisfaction with cognitive function.

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