CLINICAL VIGNETTE

Cognitive Consequences of Curative Treatment for Hodgkin's Lymphoma

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A 26-year-old male graduate student in engineering, presented with enlarged lymph nodes in his right neck area, along with drenching night sweats, in October of 2016. Aside from this new issue, he was in good health with no co-morbidities. A core biopsy of his cervical lymph node was highly suspicious for classical Hodgkin lymphoma. The patient was referred to us for oncologic evaluation. Staging for Hodgkin's lymphoma was started and he was also underwent full excisional biopsy of his lymph node, for definitive diagnosis. A PET/CT scan revealed multiple masses in the lymph nodes of the neck, chest, and anterior mediastinum (3.1 x 11.5 x 12.9 cm) and a SUV of 15.1. The excisional biopsy of the right neck lymph node confirmed diagnosis of nodular sclerosis Hodgkin lymphoma. A bone marrow biopsy revealed no involvement of the bone marrow. His final stage was Stage IIB, with bulky disease.

Next, baseline echocardiogram and pulmonary function tests (PFT's) were done, in addition to being referred to fertility specialist for sperm banking. The patient was then started on combination chemotherapy, with doxorubicin, bleomycin, vinblastine, and dacarbazine regimen (ABVD). After his second cycle, the anterior mediastinal mass decreased to 2.2 x 6.3 x 6.4 cm with a SUV of 2.2. Echocardiogram and PFT's, were repeated after every 2 cycles and remained normal with a stable ejection fraction (EF) and diffusing capacity of the lungs for carbon monoxide (DLCO). Despite this, he developed mild dyspnea on exertion, therefore, given his good response on PET/CT, his bleomycin was discontinued after cycle #2. Upon completion of his sixth cycle, his anterior mediastinal mass decreased to 1.2 x 4.4 x 5.4 cm, with a SUV of 1.7. There were also no remnants of activity in other lymph nodes. His symptoms of dyspnea resolved, and he returned to his baseline activities within 2 months of completion of his chemotherapy. In addition, he was able to finish his master degree in engineering, with honors.

A growing number of studies have reported that chemotherapy and adjuvant therapies may impair cognitive functions, with some cognitive changes persisting in a subset of cancer survivors.[1,2] The effect of adjuvant chemotherapy treatment is linked to decreased function in multiple facets of cognition, mainly including areas like attention, concentration, language, motor skills, multitasking, verbal memory, and visual memory.[3-5] The effect of chemotherapy on areas of cognition is known colloquially as chemo-fog or chemo-brain.[6] Researchers have used a battery of neurological and psychological tests on cancer patients to assess cognitive functioning. The most common and persistent cognitive deficiencies reported were in the domain of frontal lobe function. These deficiencies include information processing speed, verbal memory, and working memory.[1,7,8] Common chemotherapy regimens used to treat Hodgkins lymphoma involve ABVD (Adriamycin, Bleomycin, Vinblastine, and Dacarbazine), CHOP (Cyclophosphamide/ Hydroxydaunorubicin, Oncovin/Vincristine, and Prednisone or Prednisolone), or a combination of the monoclonal antibody Rituximab (R) with either ABVD or CHOP. Baudino et al. has shown that cancer patients with lymphoma treated with either ABVD, CHOP, R-ABVD, or R-CHOP have shown decreases in cognitive function compared to controls, specifically in areas involving frontal lobe function.[8] These patients also showed significantly lower bilateral rate of glucose metabolism in prefrontal cortices, cerebellum, medial cortices, and limbic brain areas. There was a negative correlation between metabolism in these areas and number of chemotherapy treatment cycles, while there was no significant difference between chemotherapy treated patients and controls in regard to depression, anxiety, and distress.

Chemo-brain has varied duration, with some patients being affected in the short-term and others having symptoms that persist for years after treatment.[1,4,9] Shagen et al. reported patients with complete recovery from cognitive deficiencies four years post-treatment.[10] The model supported by Baudino et al. suggests cognitive decline due to chemotherapy tends to be transient, but long lasting. They posit that the cognitive deficits last for at least 6 months post treatment. Other studies also show that structural and functional changes accompany treatment with chemotherapy, with structural changes occurring both in grey and white matter.[11,12] White matter hyperintensities (WMH) can become apparent as soon as 2 months after chemotherapy treatment, and usually last between 6 months to a year.[13] WMH that last longer than a year seem to be permanent. A prospective study done by McDonald et al. found a similar trend with grey matter volume decline as the aforementioned trend.[14] Patients treated with chemotherapy had a decrease in grey matter density in bilateral frontal, temporal, and cerebellar regions, as well as in the right thalamus as soon as one month post-treatment. Partial recovery was seen in some brain areas by end of year one, as well as what the study termed persistent gray matter volume decrease. Recovery in gray matter volume was not found for patients who were not at least partially recovering by the first year post-treatment.[14] These studies imply is that the one year mark post-treatment might be a useful prognostic tool to gauge whether cognitive recovery

will occur long term. de Ruiter et al. investigated effects of adjuvant chemotherapy treatment on breast cancer survivors 9 years post-treatment to assess the long-term effects of treatment.[15] Even after 9 years, these patients had hypoactivations in the bilateral posterior parietal cortex during memory encoding and visuospatial planning tests, as well as a reduction in grey matter volume in the left posterior parietal cortex. They also showed a loss in white matter volume in regions adjacent to the parietal cortex, possibly explaining persisting cognitive deficits.

These studies raise questions about optimal ways of treating cancer patients, whether through choice of chemotherapy regimens that have minimized incidence of cognitive deficiencies, alternative treatment options, or preventative interventions. Because the exact mechanism for pathogenesis of chemo-brain is not fully understood, and causes of chemo-brain can vary from person to person, this is a difficult question. Possible mechanisms include vascular injury, oxidative damage, inflammation, direct injury to neurons, autoimmune responses, or chemotherapy-induced anemia.[16,17] Interventions that help alleviate symptoms from these mechanisms have been tried as potential treatment. These include supplementing or increasing antioxidant intake as it can decrease vascular injury causing free radicals, supplementing Vitamin E to help against age-based cognitive decline, and performing aerobic exercise as it can increase blood flow to the brain and mitigate cognitive deficits.[16,18,19]

Pharmacological approaches have had minor success in minimizing risk for cognitive issues as a result of adjuvant chemotherapy treatment. One option was the use of D-Methylphenidate (d-MPH), a compound that has been clinically shown to help with attention-deficit/hyperactivity disorder and narcolepsy.[20] Unfortunately, two separate randomized controlled trials have shown that d-MPH did not improve cognitive function in breast cancer survivors compared to controls, while it did help with chemotherapy induced fatigue.[21,22] Another pharmacological approach was the use of the psychostimulant Modafinil, which improved cognitive performance in breast cancer survivors by enhancing speed of memory, quality of episodic memory, and mean continuity of attention.[23]

At this time, more research is needed to find a more definitive treatment option to prevent or ameliorate cognitive dysfunction associated with chemotherapy treatment. The literature supports the notion that chemo-brain resulting from adjuvant chemotherapy treatment is real and requires particular care in order to help patients overcome cancer without experiencing long-term cognitive side effects. Fortunately, it has not yet affected our patient.

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