Editorial

Neurocognitive function and CNS integrity in adult survivors of childhood Hodgkin lymphoma

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With the combination of multi-modality therapy (chemotherapy and radiotherapy), childhood and adolescent patients with Hodgkin Lymphoma (HL) have close to 90% 5-year survival rates. However, survival is not without cost. Children and adolescents survivors of HL are at risk for numerous late complications of chemotherapy and radiation therapy including secondary malignancies, cardiac and pulmonary dysfunction, and psychosocial sequelae. A recent paper by Krull *et al*. suggests that survivors are also at risk for neurocognitive impairment that is usually associated and seen in survivors of cranial nervous system disease and leukemia survivors (1). Though the data presented in the paper investigates historic radiotherapy doses and modalities, it is important to consider neurocognitive deficits can exist in patients that do not receive traditional cranial nervous system therapy.

Hodgkin lymphoma survivors exposed to anthracyclines and thoracic radiation are at increased risk for cardiovascular and pulmonary dysfunction. Cardiovascular dysfunction and morbidity is attributed to anthracyclines in combination with thoracic radiation and can lead to late effects such as cardiomyopathy, arrhythmias, coronary vascular disease, and valvular abnormalities (2,3). Pulmonary dysfunction and morbidity in HL survivors is attributed to drugs such as bleomycin in combination with thoracic radiation and can lead to pulmonary fibrosis and scarring in the lungs leading to decreased oxygen delivery (4,5).

There is evidence in the literature that radiation to the central nervous system and anti-metabolite therapy has negative consequences on neurocognitive development and can lead to impairments in childhood cancer survivors (6,7). However, there is also emerging data that adult breast cancer survivors have neurocognitive deficits that include impaired memory, attention and speed of information processing that cannot be attributed to central nervous system therapy (8-10). Thus neurocognitive deficits may be seen in patients that were not treated during critical periods of growth and development.

Krull *et al*. presented data from the Childhood Cancer Survivor Study that examines neurocognitive effects in HL survivors thought to be secondary to cardiopulmonary dysfunction from late effects of chemo and radiotherapy. The authors presented data from literature in non cancer populations that show an association between diminished cardiovascular and pulmonary health and neurocognitive integrity. Cognitive impairment in adults with chronic heart failure is a recognized factor contributing to the complexity in caring for these patients (11). Non cancer patients with chronic heart disease have demonstrated problems with executive function such as attention and processing speeds; other studies have shown that patients that have vascular compromise are at increased risk for cognitive impairment and higher risk for dementia in the future (12,13). In addition, poor pulmonary function leads to decreased oxygen supply in the brain and has been correlated with an increased risk of stroke, leukoencephalopathy and neurocognitive impairment in the non cancer population (14).

Though the study from the researchers at St. Jude's Children's Research hospital has limitations that include a small sample size and examination of a therapeutic modality that is outdated (mantle radiation), it does raise the question of whether neurocognitive testing should be undertaken in HL patients and survivors. In the past, neurocognitive function was assessed in patients that were being treated for central nervous system tumors and for leukemia as we knew that radiotherapy, intrathecal medication and anti-metabolite therapy contributed to neurocognitive dysfunction. This study presents information that perhaps neurocognitive dysfunction is more prevalent than we previously knew and may occur in patients treated at older

ages. Due to the small size, the study was unable to examine the contribution of different chemotherapy agents such as doxorubicin and bleomycin on neurocognitive effect. It is difficult to examine and attribute neurocognitive deficits to mantle radiation in a small sample size, but this study does lead to the observation that patients treated with therapy outside of cranial radiation and anti-metabolite therapy may be at risk for deficits in executive function. Previous studies have demonstrated that neurocognitive impairment can be associated with limited functional outcomes including attainment of higher education and unemployment (6,7) thus discovering that an individual may have deficits in executive function has consequences that can leave an impact on a cancer survivor.

Currently, the experts and task forces at the Childhood Cancer Survivor Study (CCSS) and the late effects task force of Children's Oncology Group (COG) implement and update the data on cancer therapy toxicities in childhood cancer survivors and help design evidence based long term toxicity screening guidelines. The guidelines currently ask for neurocognitive testing in those survivors who received cranial spinal radiation and or anti-metabolite therapy; but perhaps there are others that may benefit. In order to address issues regarding neurocognitive issues in HL patients treated in the modern era with reduced intensity, larger prospective studies need be done. Hopefully, a larger prospective trial will help us understand the effects of chemotherapy and radiotherapy on patients who do not receive cranial nervous system therapy.

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Footnote

Conflicts of Interest: The author has no conflicts of interest to declare.

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