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LETTER TO THE EDITOR

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Cranial radiotherapy and effect of aromatase inhibitors on cognitive disorders

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Dear Editor,

The main hormone related to the development and progression of breast cancer is estrogen. Resection of the ovaria to cause regression of breast cancer has been demonstrated for the first time about a century ago [1]. It is known that, about two third of the patients having breast cancer diagnosed in postmenopausal period are hormone dependent and require estrogen for tumoral growth, and that breast cancers expressing estrogen and progesterone receptors have a higher risk of relapse compared with those non-expressing. Based on this information, it is still a current opinion that elimination of estrogen in the treatment of breast cancer will block tumoral growth and prevent metastases [2,3]. There are two main approaches in order to antagonize these effects of estrogen in tumoral growth including either decreasing the levels of estrogen or inhibiting the interaction of estrogen with its receptor. Therefore, endocrine therapy has become a primary systemic and target-oriented treatment method in hormone-dependent breast cancers [3,4].

Numerous aromatase inhibitors (AI) have been developed and used in the past two decades. In clinical practice, AIs are used as an adjuvant treatment in patients with early stage breast cancer who have positive postmenopausal estrogen and/or progesterone receptor, as prolonged adjuvant therapy and as the first line treatment in female patients in postmenopausal period with metastatic or locally advancing stage hormone receptor (+) or unknown hormonal receptor status [2, 3]. AIs inhibit aromatase enzyme which is involved in the end step of estrogen biosynthesis by competitively binding to the hem in the center of cytochrome P450 enzyme; preventing peripheral transformation and aromatization of estrogen and decreasing the levels of circulating estrogen.

It has been reported in various studies including large randomized controlled studies that, AIs affect cognitive functions [3,5]. For learning, memory and normal sexual behavior, estrogen biosynthesis is needed in the brain which in turn requires expression of aromatase enzyme. Aromatase enzyme is found in different regions of the brain such as hypothalamus, prefrontal cortex, amygdale and limbic system that provide control of reproductive functions [4].Altered cognitive functions at different stages of menstrual cycle indicate that cognitive functions may depend on optimal level of estrogen. With the finding of hormone replacement therapy delays memory loss in the postoperatively developing menopause or in women having age-related loss of memory, effect of estrogen on cognitive functions has become more attractive. Decreased levels of estrogen postmenopause has been associated with the loss of cognitive abilities, increased depressive symptoms, progression of neurodegenerative diseases such as Alzheimer and dementia and the other psychological disorders [1,4,5].

Radiotherapy on a part or complete of the cranium is used as the main method in cerebral metastases of breast cancer. Formerly, therapeutic feature of RT which plays a crucial role in the treatment of local tumors has been limited with the normal tissue tolerance. In recent years, advancement in computer technology and radiologic imaging has paved the way for significant developments and innovations in the administration of RT. Today longer survival time is provided owing to effective treatment methods including advanced imaging systems, selection of the new molecular therapeutic targets in cancer patients, finding of the new ways to deliver drugs to the central nervous system, elaboration of local treatment methods such as radiosurgery and surgery.

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Both cranial radiation exposure and the other treatment methods applied are known to cause major health problems as side effects such as cognitive disorders and leukoencephalopathy. Cognitive dysfunctions occur as a result of damage that may be developed in the hippocampus. Hippocampus has a complex nature and is in close relationship with many regions found in the brain, making function difficult to define. Hippocampus which has a critical role in learning and memory processes and transition of memories to the long term from the short term memory is where newly acquired information is stored and neurogenesis occurs [6-10].

Each tissue has different sensitivity to radiation. Because central nervous system is metabolically active, it is highly sensitive to both low and high-dose radiation. In addition, since level of antioxidant enzyme is relatively lower in the neural tissues of the central nervous system, sensitivity to radiation is increased. RT-induced severe functional damage mostly emerges at high doses [7,8,10]. Until recently, it was thought that new neurons are not formed in normal adult brain or damaged regions are not renewed. However, recent studies have demonstrated existence of self-renewing cells with multipotent features in the subependymal layer which is close to gyrus dentatus of the hippocampus and subventricular region of the lateral ventricles. Several conditions including radiotherapy, chemotherapy, environmental factors, ischemia, drugs and some psychological events trigger the occurrence of neurogenesis in stem cells [9,11,12].

Despite numerous studies have been conducted on this topic, yet a sufficient advance could not be achieved regarding how to prevent damage occurring in the hippocampus or how to treat the damage developed. In light of our current knowledge, there are two ways in order to prevent the damage that would occur in the brain. First is the administration of optimal therapeutic dose to tumors through external RT techniques such as volumetric-modulated arc therapy, helical tomotherapy and intensity-modulated RT, while providing maximal protection in the hippocampus and sparing cognitive functions. In order to confirm beneficial effects of hippocampal sparing brain radiotherapy on neurocognitive functions, results of the ongoing phase II and phase III studies are needed, although today creating hippocampal sparing treatment schedules is technically and dosimetrically feasible, providing appropriate irradiation of target volumes. The second way is administration of neuroprotectants [9-12].

In conclusion; as a positive response to radiotherapy, survival is increased, although cognitive disorders manifesting in the chronic period as adverse effects of RT are known to pose a major health problem. Degree of the biological damage may vary depending on several factors such as the dose of fractions, total dose, duration and concurrently given hormonotherapy. Both aromatase inhibitors and cranial radiotherapy performed are suggested to be followed up in breast cancer patients in terms of the side effects, especially congitive functions. Concurrent or subsequent use of radiation with these drugs may increase the frequency and severity of toxicity since normal tissue tolerance will be decreased. Studies and analyses that will be conducted on this subject will light our way for evaluation of side effects.

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