Can Antidepressants Act as Potential Pro-neoplastic Agents in Patients with Neurotrophic Factor-Related Cancers?

To the Editor: ***April 28, 2008***

The prevalence of major depressive disorder is estimated to be 40% in patients with cancer, and this is a 2- to 4-times higher frequency than that in the general population.[1] Long-term, adequate antidepressant treatment is thought to be the most effective way to treat cancer-related depression, and the response rate has been reported as high as 80%.[2] Although antidepressants have long been accepted as efficacious and safe treatments, some potential adverse effects may be overlooked and we would like to remind clinicians to remain vigilant for potential adverse effects when prescribing antidepressants for cancer patients.

The therapeutic mechanism of antidepressants centers on the restoration of deficits in depression-associated neurogenesis through an increase in growth factors, and this is considered to hold for most of the contemporary antidepressive agents.[3,4] Out of all of the recognized growth factors, brain-derived neurotrophic factor (BDNF) and its receptor, the tropomyosin receptor kinase B (TrkB), may play a central role in the pathogenesis of major depressive disorder and the therapeutic mechanism of antidepressants.

In rodent models, repeated administration of an antidepressant resulted in elevated levels of BDNF mRNA and associated proteins in several brain regions, namely the hippocampus and prefrontal cortex.[5,6] Chronic use of antidepressants also elicited the expression and activation of TrkB in the same areas.[4,7] In humans, it has been determined that BDNF expression was increased in the hippocampus of subjects treated with antidepressant medication at the time of death, compared with untreated controls.[8] It is believed that most antidepressants, despite their primary therapeutic class of action, share an ability to augment BDNF production and up-regulate TrkB signaling.

Given that the BDNF-TrkB pathway acts as a potent neurotrophic signaling system through neuronal maturation, this signaling cascade has been suspected and subsequently confirmed in the tumorinogenesis of various cancers of neuroectodermal origin (eg, neuroblastoma, glioneuronma, astrocytoma, ependymoma, ganglioneuroma, paraganglioma, phaeochromocytoma, and melanoma).[9,10]

BDNF and TrkB also contribute to survival cues and rescue from chemotherapeutic agent-induced cell death in neuroblastoma cells in vitro through activation of the phosphatidylinositol-3 kinase - protein kinase B signaling cascades. For example, the addition of BDNF protects human neuroblastoma cell lines from apoptosis induced by cisplatin, doxorubicin, etoposide, and vinblastine.[11]

Given that antidepressants are responsible for the enhancement of BDNF-TrkB signaling and this pathway has been implicated in several types of malignancies, we hereby hypothesize that antidepressants may act as potential pro-neoplastic agents and therefore actually worsen prognosis in patients with neurotrophic factor-related cancers. In addition, although this hypothesis has been formulated on the basis of the BDNF-TrkB cascade, recent work has also suggested that vascular endothelial growth factor may also contribute an antidepressant effect.[12] Vascular endothelial growth factor is notoriously involved in angiogenesis and tumorigenesis,[13] it may also be implicated in an antidepressant-induced cancer risk and this should also be considered. Supporting evidence for this hypothesis may come from Brandes and colleagues,[14] who reported that antidepressants, fluoxetine and amitriptyline, can promote growth of melanoma in rodents at clinically relevant doses.

Given that antidepressants are so commonly used in cancer patients, it is of significant public health importance that their effect on tumor recurrence rates, tumor size and degree of

https://doi.org/10.1017/S1092852900016941 Published online by Cambridge University Press

metastasis is fully explored in patients with neurotrophic factor-related cancers.

Sincerely,
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Disclosures: The authors do not have an affiliation with or financial interest in any organization that might pose a conflict of interest.

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https://doi.org/10.1017/S1092852900016941 Published online by Cambridge University Press

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