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Contact: Russell Vanderboom, PhD
vanderboom@aacr.org
215-440-9300
American Association for Cancer Research

Botox could help target resistant tumors for treatment

The cosmetic treatment Botox may have a new use as an adjuvant to cancer therapy, providing an open door for chemotherapy and radiation treatments, according to a study published in the Feb. 15 issue of Clinical Cancer Research.

The study in mice, led by Bernard Gallez, Ph.D., professor of pharmacy at the Université de Louvain in Brussels, Belgium, found that by injecting Botulinum neurotoxin type A into two types of mouse tumors, the tumors' cellular vasculature opened, allowing for more effective destruction of previously resistant cancer cells. The study is the first to test the idea of using Botox against cancer and explores the possibility of its use as an adjuvant, assisting the effective delivery of chemotherapies and radiation.

The findings mark a relatively new area of cancer research, which focuses on briefly opening blood vessels that feed tumor cells in order to better deliver therapeutic agents. Until recently, much cancer research has focused on the opposite: reduction of blood vessel growth, which starves tumor cells of nutrients.

"Tumor vasculature is targeted by several advanced anti-cancer approaches that may appear contradictory," said Gallez. "Anti-angiogenesis and anti-vascular targeting are methods aimed at destroying the vessels that feed tumors, thereby depriving them of oxygen and nutrients.

"In contrast, pro-vascular approaches increase tumor perfusion and oxygenation temporarily."

While chemotherapy and radiation treatments have remained the standard of care, tumor cells of most cancer types have shown increasing resistance to therapies. This phenomenon has resulted in more toxic dosages of chemotherapy and radiation, and increased efforts to develop more drugs to which tumors don't show resistance. To

increase the efficacy of anti-cancer treatments, the new study examined strategies that transiently opened the tumor vascular bed to alleviate tumor hypoxia.

"Hypoxia is a source of resistance to radiotherapy, and is a determining factor in the poor prognosis of tumors to cytotoxic treatments," said Gallez. "Botulinum toxin could lead to inhibition of contractions of tumor vessels, improve tumor perfusion and oxygenation, and enhance the response of tumors to radio- and chemotherapy."

Botulinum toxin is a naturally occurring molecule, and historically has been implicated with intestinal poisonings. It has been developed for several clinical applications, including facial spasms, strabismus (a disease of the eye muscles), and other muscle hyperactivity. It also has become popularly known as Botox for its cosmetic uses on the face.

The toxin acts on the nervous system by blocking the release of neurotransmitters, particularly acetylcholine and norepinephrine. Gallez and his colleagues hypothesized that since Botulinum toxin impeded neurotransmitter release in the sympathetic nervous system, it could prevent neuromuscular contractions of vessels in tumors. The inhibition of this contraction could literally open the gate to improved tumor perfusion by chemotherapeutic drugs and oxygenation that enhances radiotherapy.

The scientists used two tumor models, one for fibrosarcoma and the other for mouse liver tumor. Botox was injected into the tumor once it had grown to about 6 mm. The tumors were then examined for three days, for vascular and perfusion changes as well as responses to anti-cancer therapies. In tests on oxygenation, cellular oxygen pressure was shown to significantly increase after treatment by Botox in both types of tumors. In tests on perfusion, magnetic resonance imaging results (MRI) showed significantly greater perfusion in treated mice after three days.

In addition, Botox "pre-treatment" led to significantly greater delays in tumor growth as well as stimulation of apoptosis (programmed cellular death) when compared by irradiation without Botox. The combination of Botox and the chemotherapeutic agent cyclophosphamide showed significantly stunted tumor growth after three days, as well.

Since Botox is used in clinics without serious toxicity, the study indicates the possibility for human trials. In addition, dosages used in the mouse study were within the range used with humans in clinical settings. The toxin is administered inside the tumor with

very limited diffusion into normal tissues, which may limit the amount of damage to normal cells in proximity to the tumor.

"This is the first experimental model demonstrating how Botox can affect the reaction of blood vessels that feed tumors," said Gallez. "Tumor microvessels are formed hastily, and lack smooth muscle layers, but one can find mature blood vessels, with smooth muscle layers that respond to toxins like Botulinun, inside tumors. Several laboratories, including ours, are working on new strategies to alleviate tumor hypoxia, which sensitizes the tumor to treatment. Botox appears to offer the advantage of selectivity, absence of toxicity and persistence for a longer time than other agents that act on tumor vasculature. Further research may help us determine whether this approach would be useful to treating cancer in humans."

The Gallez study was conducted by Réginald Ansiaux, Christine Baudelet, Greg Cron, Jérôme Segers, Chantal Dessy, Philippe Martinive, Julie De Wever, Julien Verrax, Valérie Wauthier, Nelson Beghein, Vincent Grégoire, Pedro Buc Calderon, and Olivier Feron, all of the Université de Louvain.

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