Tetanus Shot May Improve Glioblastoma Treatment

Preconditioning the immune system with a tetanus/diphtheria (Td) toxoid significantly improved the effectiveness of dendritic cell immunotherapy and extended overall survival in a small study of patients with glioblastoma, researchers report.

The trial enrolled 12 patients who were undergoing chemotherapy following surgical removal of their brain tumors. Patients were randomized to receive an injection of either their own mature dendritic cells (DC) or Td toxoid 1 day before receiving injections of DCs grown ex vivo and loaded with Cytomegalovirus phosphoprotein 65, which is frequently expressed in glioblastoma tumor cells but not in healthy brain tissue.

Among the six patients who received the Td shot, three lived between 20 and 24 months from diagnosis, and three lived longer than 3 years—including one patient who was still alive after 9 years—compared with a median overall survival of 18.5 months in the control group (Nature 2015;519:366–9).

Notably, longer progression-free and overall survival in the Td group was associated with greater DC migration to patients’ lymph nodes, says the study’s lead author Duane Mitchell, MD, PhD, director of the Brain Tumor Immunotherapy Program at the University of Florida in Gainesville. Past studies involving DC vaccine injections have shown that only a small fraction of DCs actually reach the lymph nodes, possibly explaining why many patients do not respond well to the therapy.

“We’ve known about the potential of DC vaccines to modulate cancer for a long time, but outcomes from clinical trials to date have been relatively disappointing,” says Mitchell. “With this study, we may have revealed a relatively simple but effective way to enhance the benefit of DC vaccination that may be applicable not only to glioblastoma but also to other cancers.”

Mitchell and colleagues had postulated that the Td shot would work by inducing local inflammation at the vaccine site but were surprised to observe a systemic effect. Greater migration of DCs to lymph nodes occurred on both sides of the body even though patients received the shot on only one side.

“We realized that it wasn’t a local inflammatory response that was driving DC migration, but a memory recall response,” explains Mitchell. “Patients had been vaccinated with Td in the past, and seeing this antigen again triggered a heightened state of awareness that caused their whole immune system to be primed and ready to respond more effectively to the DC injection.”

In a parallel study in mice previously exposed to Td, the researchers discovered that certain chemokines, such as CCL3, are involved in the DC migration pathway and mediate efficient movement of cells to the lymph nodes. They also found that DC migration was less efficient in mice not previously exposed to Td, demonstrating that the animals’ memory recall response to Td was driving the enhanced migration.

Preconditioning with a toxoid to enhance tumor-specific immune responses has potential implications for treating many types of cancer.

“This strategy could be broadly applicable to cancer vaccines in general,” says Mitchell. The goal is for dendritic cells “to migrate to the lymph nodes in order to engage and activate the T cells of the immune system. We’ve shown that this may be a mechanism for getting vaccine cells to their appropriate target in order to make treatments more effective.”

Some scientists think changes in CTC count could be a more reliable biomarker. Prior studies suggest that measuring CTCs has the potential to predict survival and guide therapy in metastatic breast cancer. Although researchers have developed various approaches to pick out these rare cells, only Janssen Diagnostics’ CellSearch is FDA-cleared.

In the new study, Scher and colleagues used this assay to count blood-borne CTCs in 711 men with metastatic prostate cancer in a multinational phase III trial of abiraterone (Zytiga; Janssen). The researchers measured the participants’ CTCs, as well as other blood biomarkers, at baseline and at 4, 8, and 12 weeks.

Patients who received abiraterone plus prednisone survived 17.7 months, versus 15.1 months for the control group on prednisone alone. More importantly, when participants were stratified into low-, intermediate-, and high-risk groups based on CTC counts and blood levels of the enzyme lactate dehydrogenase (LDH), their 12-week risk classification predicted their outcome, regardless of treatment. Overall, 46% of low-risk patients survived 2 years, whereas only 2% of participants classified as high-risk were alive at this same time point.

The study suggests that “CTCs could well permit us to get ‘red light/green light’ answers for new drugs faster and more efficiently,” says Daniel Hayes, MD, of the University of Michigan Comprehensive Cancer Center in Ann Arbor. Hayes invented the CellSearch CTC capture technology but was not involved with the current study.

Future CTC-based approaches could also help identify which treatments are likely to work in individual patients. However, “that will require going beyond counting CTCs and providing more detailed molecular information, such as whether [patients] have acquired new mutations or have expression patterns that predict resistance or sensitivity to particular therapies,” says Daniel Haber, MD, PhD, a cancer geneticist at Massachusetts General Hospital, Boston, who did not take part in the research.

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