

Brain cancer study: Magnitude of post-vaccine immune response linked to clinical outcomes

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Researchers conducting a clinical trial of a dendritic cell vaccine designed to fight malignant brain tumors called glioblastoma multiforme (GBM) have found a correlation between the "intensity" of a patient's immune response and clinical outcome, according to an article in the July 15 issue of the journal *Cancer Research*.

While other studies have suggested a link, this is believed to be the first to show direct and continual proportionality between the strength of anti-tumor responses and clinical benefits in cancer patients. This also may be the first documentation of a definite immune response/patient outcome correlation that can be credited to tumor-altering therapeutic interventions.

"Fifty-three percent of patients in our study exhibited a significant vaccine-enhanced immune response. Compared to non-responders or those with limited responses, the vaccine responders had significantly longer times to tumor progression and longer survival," said Keith L. Black, M.D., chairman of Cedars-Sinai's Department of Neurosurgery and director of the Maxine Dunitz Neurosurgical Institute. Black is one of the article's authors.

The study also substantiates a finding previously reported by the researchers: Dendritic cell vaccination and chemotherapy work synergistically to improve treatment. Time to tumor progression

increased significantly when vaccination was followed by chemotherapy, compared to vaccination alone.

"No other vaccine trial in cancer patients has shown the kind of progressive correlation between immune responses and clinical outcomes that we found," said Christopher J. Wheeler, Ph.D., research scientist at the MDNSI and the article's first and corresponding author. "We looked at whether the correlation was present after vaccination alone or after post-vaccine chemotherapy. It was evident only after post-vaccine chemotherapy. This leads us to believe that while T-cell activity may not result in net destruction of the tumor it is fundamentally changing the tumor into one that is predominantly comprised of chemosensitive cells rather than chemoresistant cells."

The findings also appear to give scientists a way to more quickly evaluate future vaccine-related research.

"The demonstration that the magnitude of immune response is directly related to survival of patients gives us a very good tool or 'surrogate marker' for clinical benefit. If we can improve the immune response of our vaccine, we can anticipate that the clinical benefit will be improved as well. This allows us to fine-tune our vaccine in more of a real-time way," said John S. Yu, M.D., director of Surgical Neuro-oncology at Cedars-Sinai, principal investigator of the clinical trial and senior author of the article.

This study centered on the immune responses of 32 patients enrolled in a Phase II clinical trial. Seventeen patients had a significant positive response after three vaccinations; 15 showed no such responsiveness. Average time to tumor progression (based on when tumor volume increased by about 25 percent on MRI scans) was about 308 days among responders, compared to 167 days for non-responders. Average length of survival (based on date of death or date of last contact with surviving

patients) was about 642 days (about 21 months) among responders, compared to 430 days (about 14 months) for non-responders.

Forty-one percent of vaccine responders, compared to seven percent of non-responders, survived at least two years. All patients in the trial had longer time to progression and longer time of survival, on average, than patients undergoing standard treatment without vaccination, although their pre-vaccine disease courses were similar.

The vaccine was first used experimentally in patient treatment in May 1998, and numerous studies have been conducted to fine-tune the therapy and combine it with other cancer-killing treatments.

Upon founding the Maxine Dunitz Neurosurgical Institute in 1997, Black led the development of the dendritic cell vaccine because gliomas and other cancer cells are not readily detected or attacked by the immune system. Dendritic cells are the immune system's most powerful antigen-presenting cells – those responsible for helping the immune system recognize invaders.

When a tumor is surgically removed, proteins are collected, cultured and introduced in a Petri dish to dendritic cells taken from the patient's blood. The new, "educated" dendritic cells are then injected into the patient where they are intended to recognize and destroy lingering tumor cells. Patients receive three vaccinations at two-week intervals. A fourth vaccination is given six weeks after the third.

Source: Cedars-Sinai Medical Center

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