Outcomes of the ACT III Study: Rindopepimut (CDX-110) Therapy for Glioblastoma

Glioblastoma multiforme (GBM) is the most common primary brain tumor in adults. Standard therapy, including maximal surgical resection, concomitant chemoradiation therapy, and adjuvant temozolomide, results in a median progression-free survival (PFS) of approximately 8 months and a median overall survival (OS) of 16 to 19 months from diagnosis.\(^1,2\) Targeted immunotherapy trials are one potential method of improving outcomes for this disease.

The most common genetic alteration in GBM is overexpression of epidermal growth factor receptor (EGFR), and the most common EGFR mutation subtype is EGFRvIII. This subtype, which is present in approximately 25% of cases, is associated with poor prognosis in GBM. The mutation results in expression of a unique glioblastoma cell surface receptor that is not expressed in normal brain tissue, making it an excellent immunotherapeutic target.\(^3\) Rindopepimut (CDX-110) is an injectable peptide vaccine that specifically targets this cell surface receptor.\(^4\) A recent multicenter phase II study of this agent has been reported with promising results for GBM (ACT III).\(^5\)

The authors enrolled 65 adult patients pooled from 33 study centers with newly diagnosed EGFRvIII\(^+\) GBM who had undergone gross total resection and standard radiotherapy and were starting standard temozolomide chemotherapy. EGFRvIII\(^+\) status was confirmed with tumor immunohistochemistry and polymerase chain reaction assays. Rindopepimut was administered with intradermal injections, first in an initial priming phase and then at monthly intervals, staggered with temozolomide treatments. Patient clinical status, anti-EGFRvIII antibody titers, PFS, and OS were closely monitored. Radiation Therapy Oncology Group (RTOG) 0525 trial data were queried, and 74 trial participants with EGFRvIII\(^+\) GBM and other similar characteristics were selected to act as a historically matched cohort for comparison.\(^5\)

For patients treated with rindopepimut, the median PFS was 9.2 months (95% confidence interval, 7.4-11.3) and median OS was 21.8 months (95% confidence interval, 17.9-26.5) from study entry (ie, approximately 3 months after diagnosis; Figure). In comparison, the “matched” RTOG cohort patients showed a median OS of 16.0 months after randomization. The authors found that anti-EGFRvIII antibody titers increased >4-fold over baseline levels in 85% patients treated with rindopepimut, demonstrating robust, specific, and durable immune responses, despite concurrent temozolomide therapy. In general, rindopepimut was well tolerated: There were no fatal adverse events, no cumulative toxicity over time (median duration of rindopepimut treatment was 7.4 months), and primarily mild to moderate injection site reactions, including erythema and pruritus. Finally, a subanalysis of tumor samples taken from 10 rindopepimut patients with tumor recurrence showed that many of these tumors no longer expressed EGFRvIII.

The 3 existing phase II trials of rindopepimut (including this study) demonstrate a pooled median PFS of 12.3 to 15.3 months from diagnosis and a median OS of 24 months from diagnosis.\(^5\) We eagerly await the results of the double-blind, phase III trial (ACT IV), which will randomize patients with resected EGFRvIII\(^+\) GBM to receive either rindopepimut or a control injection.

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Periostin: A Potential Target for Glioblastoma Multiforme Treatment

Glioma cells participate in a multitude of interactions with other cells that can influence their malignant potential. Understanding these interactions is paramount.
in devising new therapeutic strategies. Of particular importance are the interactions between tumor cells and tumor-associated macrophages (TAMs). TAMs are abundant in gliomas, and the degree of TAM infiltration correlates strongly with tumor grade. Phenotypically, TAMs resemble the tumor-promoting M2 class of macrophages, as opposed to the classic M1 proinflammatory, phagocytic class. The M2-like TAMs function to suppress the immune response, secrete trophic factors, and stimulate angiogenesis, which fosters the development and maintenance of glioma cells. Glioma cells, in turn, supply signals that polarize monocytes and microglia to adopt the M2 TAM phenotype. Glioma stem cells (GSCs) are an important reservoir of cells that determine much of the pathogenesis and treatment resistance of glioma. These cells occupy a perivascular niche along with TAMs. This spatial interrelation suggests an important interaction between the 2 cell types. In their recent report, Zhou et al defined an interaction between GSCs in TAMs wherein GSCs recruit monocyte-derived M2 TAMs from peripheral blood to glioblastoma multiforme (GBM) lesions by secreting a soluble factor, periostin (POSTN). POSTN is a secreted cell adhesion protein that has previously been shown to be involved in tumorigenesis and invasion in other malignancies.

To identify factors for TAM recruitment, Zhou et al screened for candidate-secreted factors that were differentially expressed in GSCs. This revealed an upregulation of POSTN expression.
They then analyzed human GBM samples with immunofluorescence and tissue microarray and showed that POSTN is expressed in GSCs, that TAM density is highest near POSTN-expressing GSCs in perivascular areas, and that POSTN expression levels correlate with TAM density. Using bioinformatic analyses of the Toxic Substances Control Act database, they also found that POSTN levels correlated with poor survival in GBM patients. After determining the association between POSTN and TAM density, the authors then sought to establish that POSTN is capable of attracting mononuclear phagocytes, which they demonstrated in vitro with a transwell migration assay.

The importance of POSTN in recruiting TAMs in vivo in a GSC-derived GBM mouse xenograft model was examined next (Figure). Xenografts in which GSCs expressed a silencing RNA targeting POSTN were compared with xenografts in which GSCs expressed a non-targeting RNA. From these experiments, Zhou et al discovered that, compared with tumors expressing the nontargeting RNA, tumors in which POSTN was knocked down had inhibited tumor growth, diminished total TAM density, an increase in the proportion of M1-type macrophages, and a decrease in mature M2 TAMs. Furthermore, mice harboring POSTN-deficient tumors had better overall survival. Consistent with these findings, they demonstrated that tumors overexpressing POSTN progressed more quickly and had a greater degree of infiltration by TAMs. The authors then directly established the importance of TAMs in GBM pathogenesis by cotransplanting GSCs with isolated TAMs from GSC-derived tumors. They found that mice with tumors cotransplanted with TAMs had faster tumor progression and shorter survival times. Interestingly, they also observed that cotransplantation of GSCs expressing POSTN-silencing RNA with TAMs partially abrogated the benefit of POSTN knockdown, indicating that TAMs are a mediator of POSTN-stimulated tumor growth. In a comparison of GBM samples from xenografts and human GBM samples with normal brain tissue in a tissue microarray, TAMs were shown to be derived from a peripheral blood monocytes rather than microglia.

Finally, the authors showed that POSTN signaling in TAM recruitment is mediated through αvβ3 integrin and subsequent Akt signaling, which is consistent with observations in other cell types. They demonstrated that αvβ3 inhibition with an anti-integrin αvβ3 antibody results in decreased migration of U937 cells in a transwell migration assay and decreased Akt signaling in vitro. Moreover, αvβ3 inhibition led to a reduction in TAM density in vivo after GBM xenografted mice were treated with an integrin inhibiting RGD peptide (related to the antitumor agent Cilengitide) at a high dose for 5 days. This last result raises questions about a recent phase III study that failed to find a benefit to adding Cilengitide to standard of care for patients with methyl guanine methyl transferase-methylated newly diagnosed GBM. Critics of this trial and the authors of this study pointed out that Cilengitide exhibits a dose-dependent effect and that the administered dose was perhaps too low to elicit a favorable response. A recent study by Mikheev et al provided evidence that POSTN antagonizes the cytotoxicity of Cilengitide in cultured glioma cells, thereby decreasing the effective concentration, and the authors suggested that high levels of POSTN expression in glioma cells may confer resistance to this drug. In light of this assertion, perhaps therapeutically targeting POSTN itself would exhibit a greater effect than targeting its downstream integrin effector.

Collectively, the work by Zhou et al highlighted the importance of the interaction between GSCs and myeloid TAMs in the pathogenesis of GBM and identified a novel function for POSTN that is important in mediating this interaction. Their study further elucidated some of the molecular mechanisms by which POSTN acts to recruit TAMs and demonstrated in the mouse model that inhibition of POSTN in GBMs resulted in decreased recruitment of TAMs, decreased growth of GBM tumors, and better overall survival. These observations may have important implications in developing therapies that target the POSTN-mediated recruitment of TAMs, which may someday translate into improved outcomes for patients with deadly gliomas.

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