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Optimizing an effective combination of the new microtubule-targeting agent lisavanbulin with standard-of-care therapy for glioblastoma in patient-derived xenograft preclinical models

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Clinical optimization (order and timing of administration and dosages) of components in complex multimodal cancer treatments is a daunting task that requires substantial time, funds, and manpower to achieve. To accelerate this arduous process, clinical researchers have relied on mammalian models with some degree of prediction. The ultimate goal would be to perform optimization of treatment parameters in models that are akin to individual patients. In a first step toward this goal, Burgenske et al[1] eloquently describe their approach toward optimization of treatment parameters to guide the clinical development of the new microtubule-targeting agent (MTA) lisavanbulin for the treatment of malignant brain cancer using patient-derived xenograft (PDX) models.

Microtubules are polymeric tubulin scaffolding structures controlling several vital cellular functions including mitosis, intracellular trafficking, cellular migration, cell signaling, and secretion.[2] MTAs are a diverse group of chemical compounds that bind to and disturb microtubule properties. Conventional MTAs are classified into two main groups: microtubule-destabilizing agents (eg, Vinca alkaloids and colchicine) that depolymerize microtubules, and microtubule-stabilizing agents (eg, taxanes and epothilones) that polymerize microtubules. Despite having different tubulin-binding sites and effects on microtubule dynamics, most microtubule drugs elicit remarkably similar outcomes on a molecular level when used at their lowest effective concentrations. Disruption of microtubules triggers numerous cellular responses, of which the most recognizable consequence is in cells undergoing mitosis. Metaphase spindle microtubules of cells exposed to MTAs have an impaired ability to capture chromosomes, leading to mitotic arrest and eventually to spindle assembly checkpoint-induced cell death. Furthermore, cells arrested in mitosis are highly sensitive to radiation-induced DNA damage, which may confer MTAs with radiosensitizing functions when used in conjunction with radiation therapy (RT). In addition, there are other anti-cancer mechanisms of action for MTAs that are not directly affecting cancer cells, including disruption of tumor neovasculature. The mechanisms of action of MTAs for cancer treatment are ever-evolving and new microtubule disrupting drugs are discovered every year. Most of these compounds have unique molecular interactions with tubulin that prompts specific cellular functional effects that cause cell death.

Glioblastoma (GBM) is a universally fatal cancer with a short median survival. Despite decades of intensive basic and clinical research, there is still a need for an effective treatment for GBM. Current standard of care for GBM includes surgical resection followed by concomitant chemotherapy and RT followed with adjuvant chemotherapy. The DNA alkylating agent temozolomide (TMZ) is currently the main chemotherapeutic drug of choice for GBM treatment, and radiotherapy is administered focally in a fractionated regimen. The use of MTAs for the treatment of brain tumors is limited by their inherent toxicities to the bone marrow and CNS tissues in addition to their poor blood-brain barrier penetration and the rapid emergence of resistance mechanisms.

Colchicine is a well-known microtubule-destabilizing drug, however, it is not used in cancer therapy because of its high cytotoxicity. Over the years, other tubulin-binding agents that interact with the colchicine-binding site have proven more suitable for cancer treatment. One of these agents, avanbulin (BAL27862), is a novel synthetic MTA that was discovered through optimization of high-throughput screening hits with distinct effects on microtubule organization.[3] Avanbulin is a very potent inhibitor of tumor cell growth and a promoter of cell death.[3] Avanbulin's activity is associated with the activation of the spindle assembly checkpoint[4] and importantly, it is

also active in human cancer cells that are resistant to other MTAs that bind to the vinca or taxane sites on tubulin.[4] Lisavanbulin (BAL101553) is a water-soluble lysine prodrug of avanbulin[3] that has demonstrated significant antitumor activity in both oral and intravenous administration, across a divergent panel of tumor xenograft models, including models that are refractory to standard MTA.[5,6] Lisavanbulin treatment can also target the tumor vasculature, providing additional mechanisms of antitumor action[5,6] and recently, lisavanbulin demonstrated efficacy in preclinical models of glioma.[5] Because of these promising studies, lisavanbulin entered phase 1/2a clinical trials for the treatment of advanced cancer patients[7,8] and is currently under clinical investigation in IDH-wildtype GBM in combination with RT (NTC NCT03250299).

To determine how best to maximize the clinical benefit for lisavanbulin therapy, Burgenske et al[1] utilized the Mayo Clinic panel of GBM PDX models[9] to define a spectrum of sensitivity of lisavanbulin alone and in combination with current standards of care for GBM. Similar to the concept of co-clinical trials where investigators utilize mouse cancer models in parallel to clinical trials to swiftly optimize treatment regimen,[10] the work by Burgenske et al provide the foundation for ongoing (NTC NCT03250299) and planned clinical trials, which include evaluation of the efficacy of RT with lisavanbulin in newly diagnosed, IDH-wildtype GBM.

In their study, the authors first demonstrated that while avanbulin is subjected to multidrug resistance efflux system, sufficient brain concentrations of avanbulin were observed for several hours, thus supporting the use of lisavanbulin for intracranial GBM models. The authors then demonstrated a significant extension of survival in 9 out of 14 GBM PDX lines when treated with daily administration of lisavanbulin along. Using a subset of PDXs, the authors optimized lisavanbulin administration during RT and discovered that lisavanbulin deployment concomitant to RT provides significant therapeutic benefits. To better model standard of care, lisavanbulin was added to chemoradiation and adjuvant TMZ regimens. In these experiments, the authors navigated complex animal experimental demands and demonstrated that lisavanbulin significantly extended survival irrespective of O6-methylguanine-DNA methyltransferase (MGMT) promoter methylation status. Mechanistically, treatment of short-term cell explant cultures of PDXs with avanbulin revealed increases in G2/M cell cycle arrest along with apoptosis, features consistent with a microtubule disruption mode of action. Furthermore, analysis of GBM tumor sections from lisavanbulin-treated animals demonstrated results consistent with mitotic arrest as the predominant antitumor mechanism of action. Collectively, these results strongly support the integration of lisavanbulin during and after RT/TMZ and adjuvant TMZ in all patients, regardless of MGMT promoter methylation status.

Despite intensive basic, translational and clinical research, the prognosis for GBM remains grim. There have been no new FDA-approved drugs for the treatment of GBM in over a decade. A limited availability and usage of appropriate, clinically relevant mammalian model systems certainly contribute to this lack of progress. Here the authors have successfully leveraged a large GBM PDX panel that they previously developed and characterized to determine salient features of lisavanbulin that will directly inform the design of planned clinical trials for brain tumors. Expanding their work to additional PDX lines, the authors should be able to define predictive biomarkers of lisavanbulin combination therapy response to ultimately identify GBM patients who would benefit from this new therapy.

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