Editorial

HSP90 inhibitors for high-grade glioma treatment

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Comment on: Canella A, Welker AM, Yoo JY, *et al.* Efficacy of Onalespib a Long-acting Second Generation HSP90 Inhibitor as a Single Agent and in Combination with Temozolomide Against Malignant Gliomas. Clin Cancer Res 2017;23:6215-26.

Submitted Nov 13, 2017. Accepted for publication Nov 30, 2017.
doi: 10.21037/tcr.2017.12.01
View this article at: http://dx.doi.org/10.21037/tcr.2017.12.01

Glioblastoma (GBM) is the most common malignant primary brain tumor in adults. This highly aggressive tumor is difficult to treat and virtually all GBM patients succumb to the disease despite maximal surgical resection, radiotherapy and chemotherapy (1). Many chemotherapeutic agents have been tested against GBM; however the genetic heterogeneity and the diverse molecular pathology create difficulties to treat and virtually all tumors recur. Other factors that hinter the effectiveness of chemotherapeutic drugs are the presence of blood-brain barrier (BBB), which creates a pharmacological sanctuary, the presence of tumor stem cells and of several multi-drug resistance proteins, which are involved in the intrinsic drug resistance (2,3). Temozolomide (TMZ), an oral alkylating agent, is the first-line treatment for GBM. However, resistance to TMZ, controlled by the DNA repair protein O6-methylguanine-DNA methyltransferase, is a major issue (4). Thus, developments of therapeutic strategies that can potentiate the effect of TMZ are of paramount importance. To date, several studies have been performed exploring the effects of different drug combinations with TMZ for high-grade gliomas (5).

Heat shock proteins (HSP) are polypeptides-proteins, performing essential functions, among them the synthesis and folding of proteins. HSPs are not only induced in response to stress condition but are often highly expressed in various types of cancers (6). Thus, HSPs have been an object of extensive research. HSP27 and HSP90 have been found to play a critical role in GBM growth, invasion and resistance to treatment. HSP27 interacts with STAT3 and caspace-3, while client proteins of HSP90 include many oncogenic proteins such as EGFR, AKT and ERK that prohibit apoptosis (7). Thus, these HSP might be a promising target for developing therapeutics. To date, several HSP90 inhibitors exist and are undergoing clinical evaluation (8).

A recent published paper in *Clinical Cancer Research* under the leadership of Dr. Vinay Puduvalli investigated the efficacy of a second generation long-acting HSP90 inhibitor, called onalespib, as a monotherapy and in combination with TMZ against malignant gliomas (9). In that study the authors found that onalespib inhibited the proliferation, migration, angiogenic potential and survival of glioma cells. Central tumorigenesis pathways in GBM involve EGFR, AKT and ERK. Onalespib inhibited the EGFR-AKT-ERK-S6 signaling network in glioma in a dose depended manner. Since, BBB constitute a major obstacle for successful glioma treatment, the authors investigated the ability of onalespib to cross the intact BBB in non-tumor bearing nude mice. After intravenous injection of onalespib, samples from plasma and brain were collected at different time points. The results showed higher levels of onalespib in brain compared to plasma in time points more than 2 h post-injection. Similarly, by measuring the levels of HSP70, HSP90 inhibition was verified in brain tissue. Finally, the effect of combining onalespib with TMZ was investigated. The combination of onalespib and TMZ had a synergistic effect on U251 and LN229 glioma cells and an additive effect on the A172 glioma cell line. Using a zebrafish model, in which glioma cells were injected, the combination of onalespib and TMZ showed the greatest reduction in tumor burden. The combination regimen also prolonged survival in mice bearing GSC811 xenografts (9).

HSP90 inhibitors are currently evaluated in clinical trials for solid tumors (10-12). Onalespib (AT13387) in a phase I study demonstrated a satisfactory safety profile and some antitumor activity in patients with advanced solid tumors (10). This agent was also evaluated in combination with imatinib, in patients with metastatic gastrointestinal stromal tumors, however showed limited anticancer activity (12). There are currently several clinical trials under way evaluating onalespib alone or in combination with other chemotherapeutic regimens for several malignancies. Another important issue lies in onalespib's radiosensitizing properties. Spiegelberg *et al.* showed that onalespib potentiated the effects of radiation on squamous cell carcinoma and adenocarcinoma cells lines and had an excellent *in vivo* efficacy (13). Since radiotherapy with concomitant and adjuvant TMZ is

the standard of care treatment for GBM and onalespib holds a radiosensitizing effects, it would be of great interest one to explore the combination of onalespib and TMZ with radiotherapy *in vitro* and *in vivo*. Zebrafish constitute an excellent xenograft model and based on our preliminary experiments radiotherapy can be easily administered in this model (14). In summary, the report by Puduvalli and colleagues offers solid evidence of the effects of onalespib against gliomas *in vitro* and *in vivo* which combined with its ability to cross the BBB and its synergistic effect with TMZ pave the way for the development of onalespib as a novel therapeutic agent against gliomas.

Acknowledgments

Funding: None.

Footnote

Provenance and Peer Review: This article was commissioned and reviewed by the Section Editor Ning Huang (Department of Neurosurgery, The Second Affiliated Hospital of Chongqing Medical University, Chongqing, China).

Conflicts of Interest: Both authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/tcr.2017.12.01). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Cite this article as: Alexiou GA, Kyritsis AP. HSP90 inhibitors for high-grade glioma treatment. Transl Cancer Res 2018;7(Suppl 1):S1-S2. doi: 10.21037/tcr.2017.12.01