VAL-083, a N7 alkylating agent, provides a new potential treatment option for glioblastoma multiforme because it bypasses temozolomide resistance

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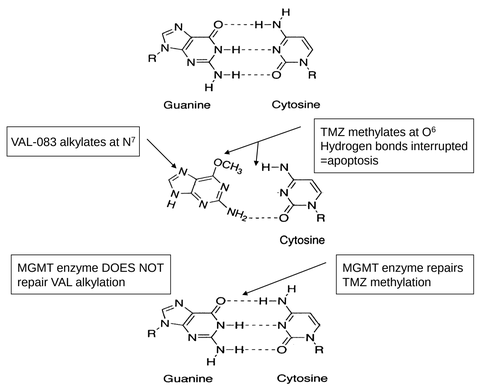
INTRODUCTION

TMZ vs. VAL-083

TMZ is the main chemotherapy used to treat GBM. However, often tumors are resistant in part through cleavage of the methyl adduct formed by TMZ which is thought to occur by MGMT. An alternative strategy is to form DNA adducts that are not repaired by MGMT. This can be accomplished using VAL-083, a novel agent that causes N7 adducts.



HYPOTHESIS

VAL-083 inhibits the growth of GBM independent of MGMT

RESULTS

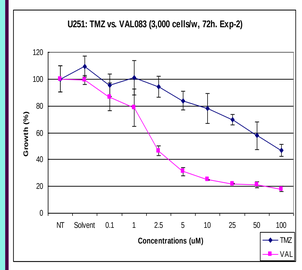
Figure 1: VAL-083 was better then TMZ for inhibiting tumor cell growth. This occurred in an MGMT-independent manner.

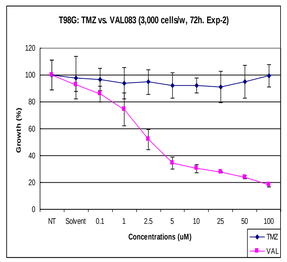
U251
Adult GBM
MGMT negative, TMZ sensitive

MGMT
Actin

T98G
Adult GBM
MGMT positive, TMZ resistant

MGMT
Actin





ABSTRACT

Glioblastoma (GBM) remains one of the most difficult tumors to treat in part because many new agents fail to cross the blood brain barrier (BBB) and secondly due to intrinsic drug resistance. Temozolomide (TMZ) is a front-line therapy for the treatment of GBM, however, it is often ineffective due to drug inactivation by O^6-methylguanine-DNA methyltransferase (MGMT). Cancer stem cells (CSC) are a subpopulation of the tumor that resist therapy and give rise to relapse. Here we described VAL-083 (VAL) a novel alkylating agent that creates N^7 alkylation on DNA, which was initially intriguing because it crosses the BBB. We addressed how it compared to TMZ, whether it could be used to overcome MGMT-driven drug resistance and if it has activity against CSCs. Addressing these questions provides further preclinical support for VAL-083, which is currently undergoing human clinical trials in the USA against refractory GBM. VAL-083 inhibited U251 and SF188 cell growth in monolayer and as neurospheres better then TMZ and caused apoptosis after 72 hrs. In a 10-day colony formation assay, VAL-083 (5uM) suppressed SF188 growth by ~80%. T98G cells are classically TMZ resistant and express MGMT, yet VAL-083 inhibited their growth in monolayer after 72 hrs in a dose-dependent manner (IC50<5 uM). VAL-083 also inhibited the growth of CSCs by 100% in neurosphere growth assays. In summary, VAL-083 has better *in vitro* efficacy than TMZ against brain tumor cells, can overcome resistance associated with MGMT, and targets brain tumor CSCs demonstrating that it has the potential to surpass the standard-of-care.

Figure 2: Pediatric GBM cells, SF188, do not express MGMT, however, they are insensitive to TMZ. The cells are, however, sensitive to VAL-083.

SF188
Pediatric GBM
MGMT negative, YB-1 positive, TMZ resistant

MGMT
Actin

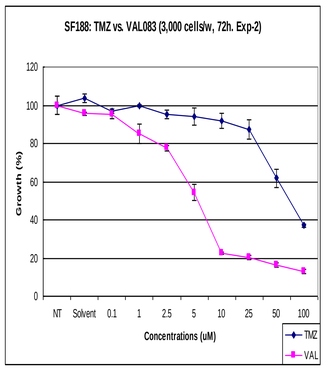
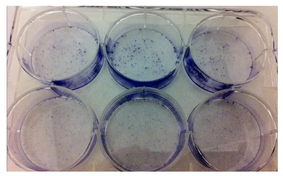


Figure 3: VAL-083 inhibits colony formation in SF188 cells after 10 days.

Control

VAL 5uM



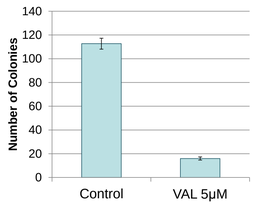
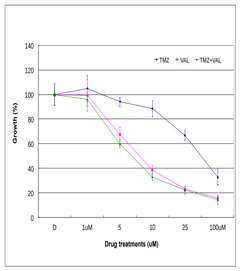


Figure 4: The simultaneous combination of VAL-083 and TMZ (1: 1 molar ratio) has little added effect on growth in monolayer or in colony formation.



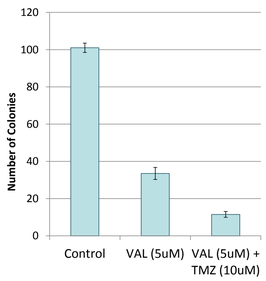


Figure 5: Brain tumor-initiating cells are thought to give rise to relapse as they are resistant to conventional therapies. Using a self-renewal assay, VAL-083 was shown to inhibit growth of SF188 cells in this assay.

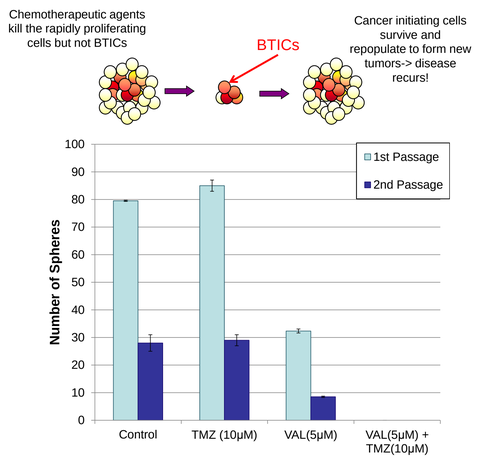


Figure 6: VAL-083 inhibits the growth of TMZ resistant BT74 cells, a brain-tumor initiating cell line.

BT74 cancer stem cells
VAL-083 completely inhibits neurosphere formation

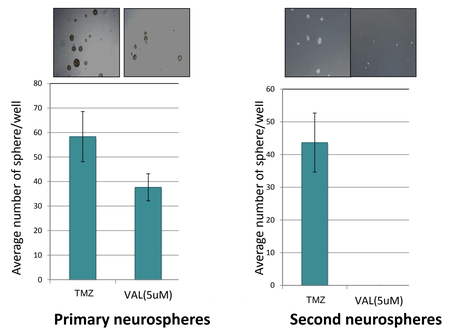
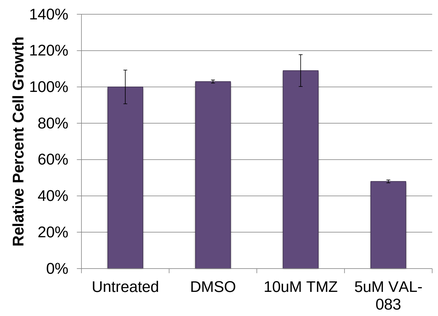


Figure 7: VAL-083 inhibited the growth of patient derived BTIC. Importantly, this patient's tumor cells were insensitive to TMZ.



SIGNIFICANCE

These data support the use of VAL-083 in refractory GBM

ACKNOWLEDGEMENTS

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