Molecular Mechanisms of Dianhydrogalactitol (VAL-083) in Overcoming Chemoresistance in Glioblastoma

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Summary: Dianhydrogalactitol (DHA) is the most common CK2 inhibitor. Standard treatments for glioblastoma (GBM) include surgery, radiation, and chemotherapy with temozolomide (TMZ). Newly, all GBM trials indicate 5-year survival is less than 3%, largely due to chemoresistance. Evidence shows that cancer cells utilize DNA repair mechanisms to counteract cytotoxic effects of chemotherapy. TMZ therapy exposes GBM to DNA damaging by inducing interstrand crosslinks (ICLs), which trigger fork stalling and activation of DNA damage response (DDR). Hyperactivation of DNA damage response DDR genes is a major mechanism conferring chemoresistance to TMZ and platinum agents. Alternative DNA damage response (DDR) pathways, particularly ataxia telangiectasia mutated (ATM) and p53, are commonly induced through ICL repair and their expression seems to vary in GBM. Dianhydrogalactitol (VAL-083) is a bifunctional agent that readily crosses the blood-brain barrier and has demonstrated activity against ATM (p53) impaired cell lines. In our previous studies, VAL-083 displayed broad anti-tumor activity against GBM cells in vitro and in vivo. VAL-083 is a potent activator of ATM and P53, which are commonly induced through ICL repair and their expression seems to vary in GBM. Our recent data demonstrate both GBM and cancer cell lines will overexpress DDR factors, which may be responsible for synergistic cell death. VAL-083 induces DDR activation/expression in GBM in a dose-dependent manner. Our data implicate a novel role for GBM cells in activating DDR factors. These findings may be responsible for synergistic cell death. VAL-083 demonstrated synergy with etoposide (topoisomerase II inhibitor) and cisplatin (alkylating agent) in GBM cell lines. Our results demonstrate both GBM and cancer cell lines will overexpress DDR factors, which may be responsible for synergistic cell death. VAL-083 induces DDR activation/expression in GBM in a dose-dependent manner. Our data implicate a novel role for GBM cells in activating DDR factors. These findings may be responsible for synergistic cell death.

MECHANISM OF ACTION

Our previous studies have demonstrated that VAL-083 inhibits breast cancer cell proliferation in a dosedependent manner and p53-independent pathway. RED48 significantly demonstrated toxicity in M059K and M059J cell lines; however, VAL-083 treatment

Figure 1: The schematic diagram describes the cell cycle progression and cytokinesis. We studied VAL-083 induction of DNA lesion formation and its effect on cell cycle progression and cytokinesis. VAL-083 in GBM cell lines (M059K and M059J) induced cell cycle arrest and cytokinesis, which was dependent on the dose.

Figure 2: Cytoskeletal effects of VAL-083 in different cancer cell lines. M059K A431 AS460

Ongoing Research and Conclusions:

1. VAL-083 displays broad anti-tumor activity in various cancer cell lines.
2. VAL-083 treatment induces DNA crosslinks leading to irreparable DNA damage and breaks, Ser1981 ATM, cell-cycle arrest and cell death in cancer cells.
3. Distinct DDR pathway in GBM and cancer cell lines will affect after effective combination therapies.
4. Clinical trials will be introduced to investigate the role of DDR pathway in GBMinduced DNA damage signaling.
5. Combination treatment with VAL-083 and chemotherapeutic agents will be tested in GBM cell lines.

References:

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Figure 3: M059K VAL-083 treatment in different cancer cell lines. M059K M059J PC3 A431 AS460

Table 1: VAL-083 demonstrates synergy with etoposide (topoisomerase II inhibitor) and cisplatin (alkylating agent) in PC3 and A431 cancer cells. The table shows CI values for the cytotoxic effect (Fa), achieved at indicated drug combinations.

Cell line Etoposide (topoisomerase II inhibitor) Cisplatin (alkylating agent) VAL-083

PC3 ED50 1.46 ED50 0.52 ED50 0.52 ED50 0.42 ED50 0.42 ED50 0.42 ED50 0.42

AS460 ED50 1.72 ED50 0.88 ED50 0.88 ED50 0.88 ED50 0.88 ED50 0.88

Titanium (topoisomerase II inhibitor) VAL-083

PC3 ED50 1.64 ED50 1.64 ED50 1.64 ED50 1.64 ED50 1.64

AS460 ED50 1.64 ED50 1.64 ED50 1.64 ED50 1.64

GBM Cell Lines M059K M059J PC3 A431 AS460

| Cell line | VAL-083 (μM) | Concentration (μM) | Fa | CI | Combination index
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Figure 4: VAL-083 treatment induced replication-dependent DNA damage. Serum starvation for 24 h before VAL-083.

Figure 5: VAL-083 pulse treatment induced replication-dependent DNA damage. Serum starvation for 24 h before VAL-083.