Phase I Trial of Genetically Modified Hematopoietic Progenitor Cells (HPC) Facilitate Bone Marrow Chemoprotection and Enabling TMZ/O6BG Dose Escalation Resulting in Improved Survival

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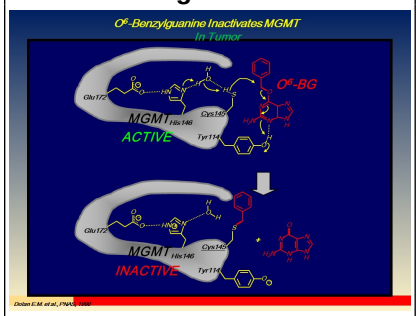
Introduction: Glioblastoma (GBM) is the most common malignant brain tumor with a median survival of 15 months despite surgery and aggressive radio-chemotherapy. The most important mechanism of TMZ resistance is the O6-methylguanine-DNA methyltransferase (MGMT) gene which repairs temozolamide-induced DNA methylation. The MGMT inhibitor O6-benzylguanine (BG) has demonstrated efficacy in depleting MGMT and maximizing tumor response in early phase clinical trials (Fig 1 A). However, because MGMT expression is also low in hematopoietic cells, this has resulted in unacceptable bone marrow toxicity, and this approach has been abandoned. We hypothesized that chemoprotection of hematopoietic progenitor cells (HPC) with an MGMT mutant (MGMT -P140K) characterized by normal methyltransferase activity coupled with low affinity for BG, would maximize anti-tumor response while enabling patients to tolerate TMZ & BG dose escalation with minimal toxicity (Fig 1B). We thus performed a phase I trial to test this hypothesis.

Figure IA



O6BG Inactivates MGMT in Tumor

Fig 1A (in Tumor)

Fig 1B: P140K-MGMT in Marrow Resists MGMT

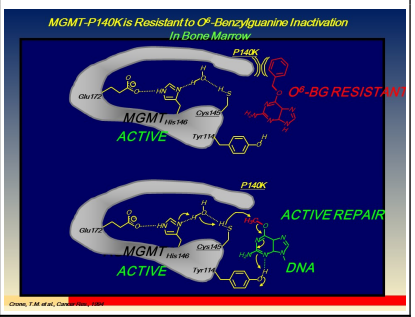
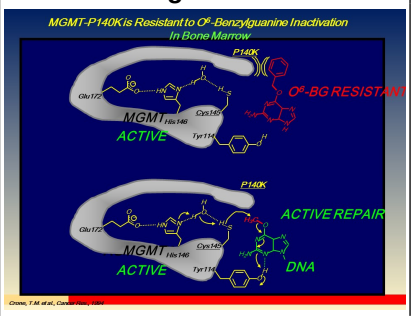
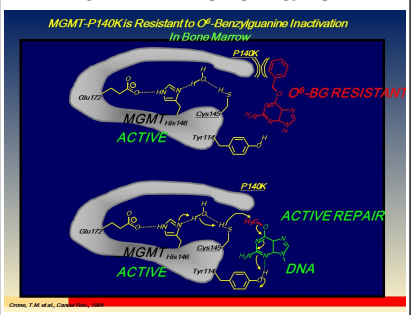


Figure 1B



MGMT-P140K in Bone Marrow is resistant to MGMT

Fib iB: In Bone Marrow



MGMT-P140K Resistant to O6BG

Methods: We treated 10 consecutive newly diagnosed GBM patients with standard surgery and radiation, followed by transplantation with autologous CD34+ hematopoetic progenitor cells engineered to express MGMT-P140K using a lentiviral vector using three different arms (Fig 3). To assess chemo-protection, patients' blood counts and transgene marking were monitored during the treatment as was tumor growth and survival.

Results: The viral transduction rates were 2.5-75% and were clearly improved in the third arm with intra-patient dose escalation (Fig 3). P140K-MGMT gene markings in peripheral blood and bone marrow cells increased 3-26-fold with only mild (Grade 2-3) mylosuppression consistent with chemo-selection and chemo-protection as hypothesized (Fig 4-5).Survival ranged from 20-36 months which exceeded their RPA predicted survival by 1.9-3.2 fold suggesting clinical benefit (mean 2.0; Fig 6).Viral insertion site analysis failed to demonstrate clonal dominance (Fig 7).

Fig 3: Chemoselection and Long-term P-140K Expression

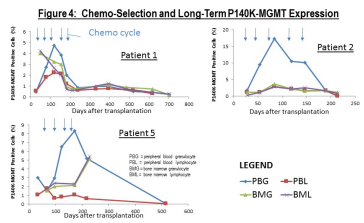


Fig 4: Mild Myelosuppression after P140K-MGMT Transduction

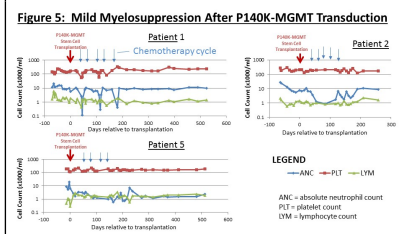


Fig5: HSC Chemoselection & P140K Expression

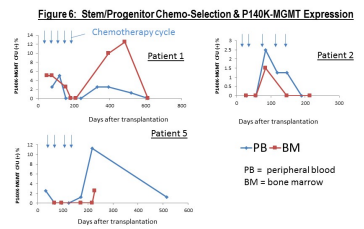


Figure 5: Partial Radiological Respons

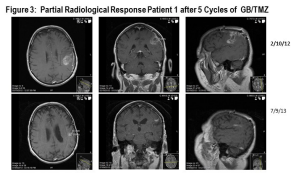


Fig 6: Radiological PR

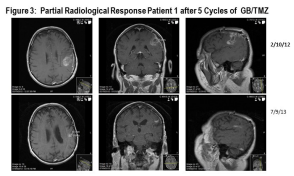


Fig 7: Unique Viral Insertion Sites

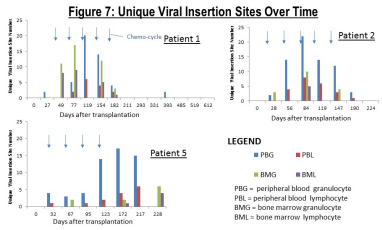
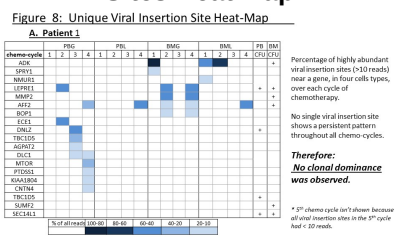
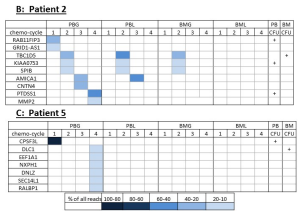


Fig 8A: Unique Viral Insertion Sites Heat Map



Patient 1

Fig 8B: Unique Viral Instertion Site Heat Map

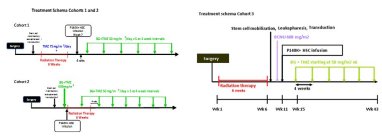


Patients 2 & 5

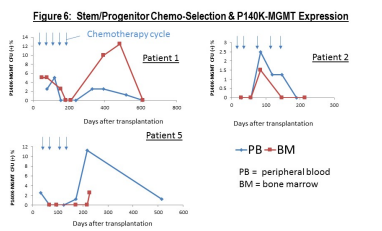
Conclusions:

These preliminary results demonstrate that this chemoprotection strategy is tolerable, safe, and facilitates TMZ & BG dose escalation resulting in increased survival. A phase II study is ongoing.

Figure 3



Three Treatment Arms

Learning Objectives:

1) Understand and explain the mechanism of action of temozolamide; 2) Explain the relationship between MGMT Promotor Methylation in GBM in Survival; 3. Describe the advantages and disadvantages of inhibiting MGMT in patients with GBM; 4) Describe the concept of chemoprotection