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Glioma trials and viral tribulations: can anything be concluded from non-controlled trials?

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The highest standard of clinical evidence is the Phase III randomized, double blind, controlled clinical trial. Their significance to clinical medicine is given theoretically by the fact that both patient and doctors are blind to the treatment and no bias can subvert patients' assignments to either treatment arms. Their practical significance is established by the fact that a large majority of potential treatments that are apparently effective in early Phase trials fail in Phase III trials. The reasons for failure of Phase III trials are multiple. From the clinical translation of potential therapies of doubtful significance even in animal models, the clinical testing of drugs that were only tested *in vitro* during preclinical development, to inadvertent bias in patient selection in early Phase trials (sometimes mandated by the characteristics of early phase clinical protocols). [1]

Dey et al. [2] provide an in depth review and critique of the current status of the potential pathogenic interactions between cytomegalovirus and glioma. Though some groups have reported finding CMV sequences and CMV-antibody reactivity in glioma tumors, many others have failed to do so (reviewed in detail in [2]). Also, there is no published evidence of CMV replication in the brains of adult patients. In addition, as described elegantly by Dey et al. many of the preclinical data that would be necessary to consider a pathogenic role for CMV in gliomagenesis are missing. Nevertheless, a clinical trial could still provide useful new information regarding a potential new treatment, even if the basis of its effects were poorly understood. Such a trial has been performed, reported, and is the impetus for the review by Dey et al. [3,4].

As a result of a critical examination of the data supporting a role for CMV in glioma tumors, Dey et al. observe that the trial's results are reported in an unexpected manner: the authors report no effects after 6 months of treatment of patients with Valganciclovir when compared to controls, yet, upon continued Valganciclovir use, the authors detect a large effect of Valganciclovir on the survival of glioma patients. Briefly, the authors report that, when compared to a single group of contemporary controls, not within any type of clinical trial, patients appear to survive longer, the longer they are treated with Valganciclovir. How to explain the discrepancy between the double blind, randomized arm of the trial that showed no effects after 6 months of treatment, compared to impressive effects reported upon continued use of Valganciclovir, especially when Valganciclovir for the treatment of confirmed CMV infection is given for a maximum of 120 days, usually though for only 2–4

weeks. The Phase III trial (and Valgancyclovir administration) ought to have stopped after 6 months, as per the clinical trial, in order to evaluate any possible long term effects of the initial treatment. If authors suspected that lengthier Valgancyclovir administration would be therapeutic, a new extended Phase III trial should have been implemented. However, because of compassionate use, clinical investigators continued to administer Valgancyclovir to all patients after the end of the original Phase III trial. Thus, if Valgancyclovir is acting through inhibiting CMV, how is it that 6 months of treatment had no effect, yet continued treatment beyond recommended and tested clinical use in confirmed CMV infections had such a powerful effect?

A flaw in the logic used to analyze these data likely explains these results. Any group of patients will of course survive for different times; the longer a patient survives, the more Valgancyclovir he or she will have consumed. The authors then take survival data of patients that survived for six months, or that continued receiving Valgancyclovir, and conclude that the patients that were treated for Valgancyclovir the longest survived the longest. The simple fallacy is to conclude that the longer a takes Valgancyclovir, the longer they survive. In reality, the longer a patient lives the more Valgancyclovir they consumed. It is likely that the patients that survived longest also consumed higher volumes of infusions such as tea, coffee, or water. For the sake and respect to patients' lives suffering from this deadly disease, we pray that no claims will be made for the beneficial effects of tea or coffee.

References

1. Lowenstein PR, Castro MG. Uncertainty in the translation of preclinical experiments to clinical trials. Why do most phase III clinical trials fail? *Curr Gene Ther.* 2009; 9:369–374.
2. Dey M, Ahmed AU, Lesniak MS. Cytomegalovirus and glioma: putting the cart before the horse. *J Neurol Neurosurg Psychiatry.* 2014 Epub ahead of print.
3. Stragliotto G, Rahbar A, Solberg NW, et al. Effects of valganciclovir as an add-on therapy in patients with cytomegalovirus-positive glioblastoma: A randomized, double-blind, hypothesis-generating study. *Int J Cancer.* 2013; 133:1204–1214. [PubMed: 23404447]
4. Söderberg-Nauclér C, Rahbar A, Stragliotto G. Survival in patients with glioblastoma receiving valganciclovir. *N Engl J Med.* 2013; 369:985–986. [PubMed: 24004141]