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Good maths is needed to understand CMV data in glioblastoma

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To the Editor:

Söderberg-Nauclér *et al.*[1] report on a series of a trial-subgroup of 22 patients with newly diagnosed glioblastoma, treated for >6 months with valganciclovir, an anti-cytomegalovirus (CMV) agent, and standard radiochemotherapy with temozolomide. An additional 28 patients with a similar treatment received within a compassionate-use access are included in this case series.

The rational of this study is based on the observation by several groups that high-grade gliomas express CMV antigens, which has provoked the controversial and unproven hypothesis that these tumors may be caused and/or sustained by CMV infections.

Survival data are presented for the full set of selected patients and subgroups thereof with shorter or longer exposure to valganciclovir. Kaplan–Meier estimates are given in comparison to a contemporary series. These estimates suggest a median 2-year survival of 63.6% in the valganciclovir group and 17.2% in the contemporary series.[1]

This survival rates are unusual and currently unmet by any experimental treatment tested in controlled clinical trials. While there are numerous examples of favorable outcomes associated with experimental treatment in uncontrolled clinical trials, data presented in this report are in our view particularly problematic in conceptual, scientific and clinical patient-related aspects

The hypothesis-generating randomized trial conducted and published previously by the authors did not provide evidence for antitumor activity of the valganciclovir therapy.[2] This trial included patients with newly diagnosed who were randomized to receive valganciclovir or placebo in addition to standard radiochemotherapy. Progression-free survival estimates in the intention-to-treat (ITT) population were 5.6 months in the valganciclovir group and 5.5 months in the placebo group. Median overall survival was 17.9 months in the valganciclovir group and 17.4 months in the placebo group. Two-year survival rates were 27.3% in the valganciclovir group and 25% in the placebo group, respectively.[2]

Why do the authors' data from the present series[1] differ so much from the data of the ITT population in the controlled trial?[2]

The initial randomized trial aimed at a treatment with valganciclovir of 6 months and allowed crossover after unblinding. From the patient population—most likely with a progression-free survival of >6 months—irrespective of whether they had been treated with valganciclovir initially—the authors generated a new group of patients with a valganciclovir exposure of >6 months, consisting of patients with or without valganciclovir. These published patient data are supplemented with 28 patients from post-study compassionate use. This is *de facto* the creation of a new long-term benefitting subgroup of patients mixed from the original trial and further assembled patients from a compassionate use program. This patient cohort was heterogeneous with respect to standard treatment and timing of valganciclovir and—more importantly—was not adequately protected from selection bias. In fact, by selecting for patients with valganciclovir exposure of >6 months—after surgery or after 6 months of standard treatment—this cohort is deliberately enriched for favorable outcome. In our view a formal comparison with a contemporary glioblastoma cohort, which not even reaches the median and 2-year overall survival of contemporary trial data,[3,4] is not justified without prior analysis and documentation of factors known to be relevant for longer survival, such as age, resection status, isocitrate dehydrogenase mutation and methyl-guanine methyl transferase status.[5] Without information on these essential prognostic factors the Kaplan–Meier estimates presented by Söderberg-Nauclér *et al.*[1] have to be interpreted with caution.

The authors claim a prognostic impact of low- or high-grade CMV infection. It remains unclear how this was assessed. The authors performed immunohistochemistry of the CMV immediate early antigen in the tumor tissue. Set aside the fact that the expression of the IEA antigen does not constitutes an infection *per se*, high- and low-grade "infection" is not defined. In addition, it remains unclear what the status of the benefitting or non-benefitting patients is. Similarly, it would be interesting and a relevant proof-of-concept to see an anti-CMV therapy effect in the tumor tissue after therapy at recurrence. This is particularly important as potential off-target effects may be an alternative explanation for any effects of valganciclovir.

As is, the letter, but not the full article by Söderberg-Nauclér and coworkers[1,2] is already generating public interest and hope in patients and caregivers who request off-label use of valganciclovir based on an unchallenged perception of the data. With the limitations outlined, this is an undue publicity for a concept that failed in a controlled trial,[2] and is supported solely by circumstantial scientific evidence without adequate clinical validation.

Yours sincerely,
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