Response to: Comment on ‘Dexamethasone exerts profound immunologic interference on treatment efficacy for recurrent glioblastoma’

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Accessibility
Response to: Comment on ‘Dexamethasone exerts profound immunologic interference on treatment efficacy for recurrent glioblastoma’

Eric T Wong*1 and Kenneth D Swanson1

Sir,

We would like to thank you for an opportunity to respond to the comments from Drs Ellsworth and Grossman in their letter to the editor concerning our recent paper, ‘Dexamethasone Exerts Profound Immunologic Interference on Treatment Efficacy for Recurrent Glioblastoma’, by Wong et al (2015).

Contrary to the assertion by the authors, our paper did not claim that the effects of dexamethasone were mediated via steroid-induced lymphopenia. It is widely accepted that dexamethasone exerts pleotropic effects on the immune system that lead to the suppression of multiple effector systems required for the lymphocyte to fulfill all of its functions. Additionally, we have commented that it is possible that the dexamethasone was likely an important antiemetic in the premedication regimen that lead to the suppression of multiple effector systems required for immune function.

The authors also cited their work on the immunosuppressive effect of radiation and temozolomide when given to patients with newly diagnosed glioblastomas (Grossman et al, 2011). They found that 40% of patients had < 200 CD4 cells mm−3 2 months after initiation of treatment and this was associated with a poorer survival when compared with those with ≥ 200 CD4 cells mm−3. Given that corticosteroid use was not a controlled variable, it is possible that dexamethasone may have contributed to the poor survival outcome in this study. Regardless, the overall conclusion of their study was also consistent with our utilisation of T-lymphocyte counts as a marker of poor outcome. Furthermore, an earlier study by Hughes et al (2003) investigated the phenomenon of lymphopenia in the pre-temozolomide chemo-irradiation era and found that 24% of the cohort had < 200 CD4 cells mm−3 whereas 76% had ≥ 200 CD4 cells mm−3. Therefore, it is possible that the addition of temozolomide to dexamethasone plus radiotherapy increased the proportion of patients who developed poor outcome and low CD4 lymphocyte count (from 24 to 40%). Taken together, it may be important to re-examine the potential role of dexamethasone in these two studies.

Lastly, the authors also cited that treatment-related lymphopenia is a marker of poor outcome in pancreatic and non-small cell lung cancers (Balmanoukian et al, 2012; Campian et al, 2013; Tang et al, 2014; Wild et al, 2015). Our data are consistent with this contention, but do not address the cause of the low T-lymphocyte counts in our patients. It is notable that patients in these studies also received concurrent emetogenic chemotherapies, such as taxol/carboplatin, gemcitabine or gemcitabine/carboplatin, and dexamethasone was likely an important antiemetic in the premedication regimen and may therefore confound the outcome analysis. Although it is hard to absolutely devolve the contribution of dexamethasone from prior radiation and chemotherapy effects in patients with recurrent glioblastoma, the NolvTTF-100A monotherapy arm in the phase III trial nevertheless offered us a unique opportunity to evaluate the sole effect of dexamethasone dosage because the influence of prior radiation and chemotherapy was randomized and balanced. In contrast to commonly used chemotherapeutic regimens (Grossman et al, 2011), NolvTTF-100A does not exert such deleterious effects on the immune system. Given these conditions, we were able to determine that subjects who received a dexamethasone dose of ≥ 4.1 mg day−1 had a significantly shorter survival than those who took < 4.1 mg day−1. Therefore, one of the obvious implications of our work is that future clinical trials in the glioblastoma population may need to control for the confounding dexamethasone effect in outcome. Furthermore, it may be worthwhile to re-examine treatment outcomes of prior clinical trials based on dexamethasone stratification.

The authors declare no conflict of interest.

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LETTERS TO THE EDITOR

BRAF-mutated metastatic colorectal cancer between past and future

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Sir,

We read with interest the meta-analysis by Rowland et al addressing the role of BRAF V600E mutation as predictor of benefit from anti-EGFR monoclonal antibodies (mAbs) in metastatic colorectal cancer (MCC).

Authors conclude that there is insufficient evidence to definitively state that RAS WT/BRAF MT individuals attain a reduced benefit from anti-EGFR mAbs compared with RAS WT/BRAF WT ones. Their conclusion is based on the lack of a significant interaction between BRAF mutational status and the effect of the addition of an anti-EGFR mAb to standard therapies (Rowland et al, 2013).

We pinpoint some considerations are needed to properly put these results in the clinical perspective, as pointed out in our previous work (Pietrantonio et al, 2015).

First, it should be noted that in terms of PFS, where the confounding effect of subsequent lines of treatment is absent, the P-value for interaction is equal to 0.07. Of note, an alpha-error up to 0.10 is often considered reasonable for additional of an anti-EGFR mAb to standard therapies (Rowland et al, 2011) investigating BRAF ± MEK and EGFR inhibitors in molecularly selected patients (Atreya et al, 2015). Knowing BRAF status is today crucial to allow BRAF MT patients to enter clinical trials with these targeted agents.

In conclusion, although the negative predictive power of BRAF V600E mutation with respect to anti-EGFR mAbs will never be formally demonstrated in properly designed, wide and expensive clinical trials, BRAF testing is today recommended by major guidelines. In our opinion, irrespective of the presence or choice of treatment options to expose BRAF mutant patients to anti-EGFR mAbs, BRAF clearly stands as a molecular marker able to inform clinical decisions in the daily practice, and hopefully its role in treatment decisions will be better defined in the near future.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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