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LETTER TO THE EDITOR

Corticosteroids compromise survival in glioblastoma in part through their elevation of blood glucose levels

Rainer J. Klement[1] and Colin E. Champ[2]

1 Department of Radiotherapy and Radiation Oncology, Leopoldina Hospital, Schweinfurt, Germany
2 Department of Radiation Oncology, University of Pittsburgh Cancer Institute, Pittsburgh, PA, USA

Correspondence to: Dr Rainer J. Klement,
Department of Radiotherapy and Radiation Oncology, Leopoldina Hospital Schweinfurt,
Robert-Koch-Str. 10, 97422 Schweinfurt, Germany
E-mail: rainer_klement@gmx.de

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Sir,

We read the recent paper by Pitter *et al.* (2016) with much interest. In their report entitled 'Corticosteroids compromise survival in glioblastoma' they thoroughly compiled sufficient evidence to question the traditional, unquestioned usage of steroids, such as dexamethasone (DEX), in brain tumour patients to counter intracranial oedema and associated symptoms. DEX treatment prior to radiation therapy was a significant predictor of worse overall and progression free survival in three large cohorts of glioblastoma patients analysed retrospectively by the authors, a result quite robust to adjustment for other confounding factors in multivariable analysis. To gain insights into the mechanisms, the authors used a murine glioma model in which a significantly adverse effect of DEX on the efficacy of ionizing radiation could be demonstrated. DEX treatment halted tumour cell proliferation by downregulating several genes involved in spindle assembly and mitosis, and this gene signature was further shown to correlate with significantly worse survival in DEX-treated patients whose data were included in the Cancer Genome Atlas. Therefore, a major finding of this study is that DEX treatment affects one of the five radiobiological principles of radiotherapy (the so-called '5 R's'), namely the redistribution of cells in the cell cycle. By lowering the fraction of relatively radiosensitive G2/M phase cells and increasing the fraction of relatively radio-resistant G1 phase cells DEX could decrease the tumour control probability for a given radiation dose prescription.

Pitter *et al.* discuss this interference with radiotherapy as a major mechanism to explain the DEX-related detriment of survival. Also mentioned are the less likely contributing side-effects of steroid usages, such as myopathy, impaired immune function, adrenal insufficiency or bowel perforation. However, there was no mention of the most well-known and obvious side-effect of steroids, their propensity to raise blood glucose concentrations within the diabetic range (Sethi *et al.*, 2016). Steroid-induced hyperglycaemia should be a major concern given the increasing number of studies unequivocally demonstrating a worse prognosis associated with high blood glucose levels during brain cancer treatment (McGirt *et al.*, 2008; Derr *et al.*, 2009; Mayer *et al.*, 2014; Tieu *et al.*, 2015) (the latter study controlled for DEX use), and apparently cancer treatment in general (Weiser *et al.*, 2004; Lamkin *et al.*, 2009; Minicozzi *et al.*, 2013; Monzavi-Karbassi *et al.*, 2016).

Elevated blood glucose levels would contribute to radioresistance of glioblastoma cells through several mechanisms (reviewed in Klement and Champ, 2014). An elevation in blood glucose concentration leads to a proportionately higher glucose flux towards tumour cells. As glucose diffuses further than oxygen, this would particularly benefit hypoxic cells that are already up to 2.5-times more radioresistant due to the lack of oxygen-mediated fixation of DNA damage (Bertout *et al.*, 2008). These cells heavily rely on glycolysis for energy production. But even under non-hypoxic conditions, glioblastoma cells are expected to depend heavily on glucose for glycolysis and as a precursor for glutamate synthesis due to dysfunctional mitochondrial function (Seyfried *et al.*, 2015). Furthermore, the end products of glycolysis, pyruvate and lactate, have anti-oxidative properties that protect tumour cells from endogenously

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produced reactive oxygen species and other radicals, and also those inflicted by ionizing radiation. The same applies to glutathione, which is increasingly produced and regenerated by tumour cells in a glucose-dependent manner (Allen *et al.*, 2014). Accordingly, when starving tumour cells from glucose and forcing them to use mitochondrial oxidative metabolism, they experience increased oxidative stress and sensitization to radiation and chemotherapy (Allen *et al.*, 2013).

The effects of DEX on tumour cells seem to mimic the protective effects of nutrient restriction on normal cells, namely an increase in p21 and Gadd45, and thus reduction in proliferation and less vulnerability to ionizing radiation (Yamaza *et al.*, 2010). We are convinced that high blood glucose levels—through the mechanisms outlined above—additionally contribute to a further enhancement of radioresistance for tumour, but not normal cells. The latter would be better protected by inducing the physiological starvation response through fasting, calorie restriction or fasting-mimicking diets such as the ketogenic diet, for which one of us (C.E.C.) has shown to benefit glioblastoma patients by reducing blood glucose levels even with concurrent steroids (Champ *et al.*, 2014). Such metabolic strategies target a variety of pathways simultaneously; one of them is the PI3K-Akt pathway whose downregulation impairs DNA damage repair in glioblastoma cells (Kao *et al.*, 2007). In addition, in murine astrocytoma and human glioblastoma models overall calorie restriction downregulated VEGF, reduced proliferation and increased the number of TUNEL-positive cells by more than 2-fold (Mukherjee *et al.*, 2004)—effects very similar to the VEGF-antibody B20-4.1.1 found by Pitter *et al.* as superior to DEX treatment. However, in contrast to this antibody, metabolic therapies have been shown to additionally increase radiosensitivity of tumour cells (Klement and Champ, 2014). While these findings illustrate the need for other agents besides DEX to treat cerebral oedema, the unfavourable metabolic environment created by DEX further illustrates that the exploration of metabolic treatment strategies should receive more attention among the radiation oncology and cancer treatment community.

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