

Short Communication

A New Glioblastoma Treatment, Potentially Highly Effective, Combining Focused Ultrasound Generated Hyperthermia and Radiations

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Abstract

To treat Glioblastoma, we recently proposed the use of hyperthermia plus radiation. Hyperthermia was generated by a transcranial, MR guided, high intensity focused ultrasound device (TcMRgFUS). To obtain this result, minimal modifications of this device, primarily conceived for small volume ablation, were required, in particular reduction of the single-pulse power and a change of the pulse shape. In this paper we discuss the main characteristics of the proposed method and review possible improvements.

INTRODUCTION

Glioblastoma (GBM) is the most aggressive tumour of the central nervous system, corresponding to grade IV of the World Health Organization's classification [1]. This kind of glioma is the most common primary brain tumour in adults. The incidence is about 3 per 100,000 person-years in USA, the median survival time is of about 15 months after diagnosis [2] and 12 months after first resection [3].

The invasive nature of GBM into the perivascular space has recently been demonstrated [4]: in this way the tumour doesn't need, for its growth, to create a new network of blood vessels (aka angiogenesis). GBMs recur in more than 90% of patients, usually centrally [5]. The current standard treatment includes external-beam radiotherapy (EBRT), maximal surgery, and chemotherapy with temozolomide (TMZ). Early Phase II clinical trials using bevacizumab, a monoclonal antibody against VEGF, in both newly diagnosed and recurrent high-grade gliomas (HGG) showed promising results, but these have not been confirmed in recent Phase III trials [6]. This seems consistent with the quoted direct access of the tumour to the normal microvascular vessel 'tree'.

Treatments that include EBRT result in a significant increase in patient survival [7]. Dose escalation studies have demonstrated survival improvements up to an overall dose of 60 Gy [8,9], generally with 2 Gy/day fractionation, 5 days a week for 6 weeks

(60 Gy total dose). Beyond this dose there is only a minimal increase in survival at the cost of potentially severe toxicity [10]. The study by Elaimy et al. [11], supports the use of stereotactic radio surgery (SRS) either to boost EBRT treatment or to treat small-volume recurrences.

There are ongoing studies of immunotherapy in patients with GBM, including preliminary work with a tumour-specific vaccine-targeting epidermal growth factor receptor variant III (EGFRvIII) which is a constitutively activated and immunogenic mutation widely expressed in GBM [12]. Tumour heterogeneity and the aggressive nature of GBM affect also the potential success of immunotherapy. However, targeting cytomegalovirus pp65 by using dendritic cells, very impressive results are recently obtained on a small cohort of eleven patients of newly diagnosed GBM [13]. Different combination strategies may also produce significant gains in patient survival [14]. Transcranial high-intensity focused ultrasound with MR guidance (TcMRgFUS) has the potential to be an important weapon for intracranial therapy [15], in particular as an ablative device at higher frequencies (650 kHz) [16,17] that can open and close the Blood Brain Barrier (generally at lower energies and with the use of contrast media) both with external [18-20] and implantable transducers [21]. In this way a greater absorption of chemotherapeutic drugs in the tumour is obtained.

In this complex panorama, we decided to explore how to combine TcMRgFUS generated hyperthermia with radiation [22];

we review here the main aspects and possible improvements of the technique.

MATERIALS AND METHODS

The slowing down effect of radiations, stem cell hypothesis, hyperthermia

The quoted radiobiological data demonstrate the high resistance of glioblastoma to radiation. Still, the data are not sufficient to explain the unsatisfactory clinical results. In fact, like other tumours, glioblastoma exhibits an “adaptive response”: the effect of radiation on tumour cells is not only small but decreases as the treatment progresses [23]. There is increasing evidence that solid tumours are hierarchically organized and contain a small population of cancer stem cells (CSCs) [24,25].

The subpopulation of CSCs has the capability of self-renewal, an unlimited capability of proliferation and a tendency to recur [26], differing from non-stem cells (CDCs). *In-vitro* and *in-vivo* experiments have shown that glioma CSCs are significantly more resistant than normal, differentiated cells [27].

In particular, the three human glioma cell lines (U-87MG, U-138MG, U-373MG) have a large capacity to recover from potentially lethal radiation damage. Since hyperthermia causes radio sensitization and inhibition of recovery from radiation damage, its combination with radiotherapy creates a potent combination for treating human brain tumours [23,28-31].

In fact the Raaphorst et al. [29], survival curves obtained with an hyperthermic treatment of 15 min at 45°C (CEM43 = 60 min) were nearly super imposable on those due to carbon ions from Ferrandon et al. [32].

Potentially therefore, TcMRgFUS generated hyperthermia combined with radiation is the perfect weapon, but the critical parameter is the time between the two applications: the maximum effect is obtained when the applications are simultaneous, but by increasing the delay time, the effect is progressively reduced. For a simulation, we choose 1 and 2 hours delay to allow the patient to be moved to and re-positioned in the second treatment room.

The use of a MRgFUS as an hyperthermic device

In a recent paper, Coluccia et al. [16], described the first successful non-invasive thermal ablation of a brain tumour with transcranial magnetic resonance-guided focused ultrasound (TcMRgFUS).

This paper reported a tumour recurrence in the left thalamic and sub thalamic region after surgery for a posteromedial temporal lobe GBM. A total of 25 sonication was applied (17 over the heat ablative threshold); the total sonication time was more than 3 h and about one tenth (0.7 cm³) of the total enhancing tumour volume (6.5 cm³) was ablated with an Insight ec MRgFUS Exablate Neuro system [31]. The single ablation volume was about 0.041 cm³ = 41 mm³ imagine a small cylinder of 3.6 mm in diameter and 4 mm in height), while the average ablation efficiency was 0.7 cm³/180 min = 3.9.10⁻³ cm³/min = 3.9 mm³/min.

The single pulse lasted 10 - 25 s and transmitted 150-950 watts of acoustic power into the targeted tumour tissue, where

acoustic attenuation is converted into heat, considering that the main absorption comes from skull bone (30-60 times that of the soft tissue [33]). So a cooling period of around 80-90 minutes is required after each sonication to prevent adverse thermal lesions in the skull bone, the adjacent tissue, and the meninges. Considering that the tumour volume can be of the order of 90 cm³, only an extraordinary (and improbable) increase of the MRgFUS device power could enable the system to ablate a whole tumour.

A possible solution would be to drastically reduce the pulse energy, going from ablation (about CEM43 = 1000 min) to hyperthermia (CEM 43 - 60 min), drastically reducing the pulse time to about 7-8 seconds with an average temperature of about 52°C. That could yield the required CEM 43 of about 60 min.

With such a short time the warming of the whole tumour reported by Coluccia et al. [15], can be obtained in the reasonable time of about 1.5 hours, also allowing a 20 s cooling time between the sonications. Then we have to transfer the patient to the radiation room for the second treatment.

RESULTS AND DISCUSSION

Considering the MRgFUS device as an hyperthermic one, not one tenth but the whole tumour can be treated and several combined protocols are allowed. Taking into account the complexity of patient positioning and standard MRI image acquisition, we propose, in particular, a treatment in which both hyperthermia and radiation are given only once weekly, with a radiation dose of about 5 Gy each time.

The whole treatment would last 6 weeks, with a total radiation dose of about 30 Gy. Compared with “standard” radiation treatments, the strong synergy between radiation and heat allows us to make the total dose very low. For the patient, this would be a very “gentle” treatment.

On the other hand it would be extraordinarily effective. A standard radiation treatment ($\alpha = 5.4 \times 10^{-2} \text{Gy}^{-1}, \beta = 4.2 \times 10^{-2} \text{Gy}^{-2}$) 2 Gy/day, 10 Gy/week, 6 weeks of treatment for a total dose of 60 Gy [29]) would result in a minimum value of the clonogens of about 3.61×10^{-4} and a time to regrow the tumour to its initial volume of 2.29 years [29]. Due to the “adaptive response” and stem cell effect, the median survival is less than one year [34]. In contrast, the proposed treatment, with a one hour time delay, would result in a minimum value of the clonogens of less than 10^{-7} and a time to regrow of the tumour at the initial volume of 4.5 years. With 2 hours delay the minimum value of the clonogens becomes less than 10^{-6} and a time to regrowth of the tumour to its initial volume of 3.9 years [22].

Considering the low minimum value of clonogens and the hyperthermia stimulation of the immune system [35], we could expect an even better result. In particular the possible tumour-protective effect of heat shock proteins is low if the time interval between the treatments is short and may reach its maximum 16 hours after the heating [36].

There remain (at least) two problems. One is the total time that the patient needs to stay in the MRI system. An important improvement could come from ‘painting’ the heat dose over the target volume by the movement of the focal spot [37-40]. Another linked problem could be the excessive bone warming, potentially

inducing pain in the patient and then requiring longer cooling times. Our proposed therapy [22] would administer to the patient about half the total "Equivalent Thermal Dose" respect to the quoted ablative therapy [16], so that a significant bone warming is not expected, at least for the considered, centrally located, small tumour.

In addition, it is important to consider the evolution of GBM. Several GBM models [41-43] predict that in the evolution of the disease, the biologically active (proliferating and infiltrating) region is pushed away from the tumour core, in a region bordering the central part, that becomes progressively larger and necrotic. Therefore, it seems reasonable to concentrate both radiation and hyperthermia in this more external region. This would change radically the current GBM treatment planning, in which the maximum of the dose is located in the tumour centre, and would reduce significantly the volume of the region to be heated (and irradiated).

In light of the above, there is significant room for improvement. The proposed technique could radically improve the current GBM cure rate. Experimental verification is therefore urgently desired.

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