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Case Report

Treating Aggressive Brain Tumors with the Combo Bumetanide/Mebendazole: A New Cytotoxic, Anti-Invasive Network Strategy

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Abstract

Despite much progress in aggressive brain tumors, we are still failing to provide efficient cure. This is due to the complexity of brain tumors, their heterogeneity& plasticity, and the neglected peritumoral microenvironment generated hyperactivity that facilitates metastasis.

We have tested the effects of a combo of 2 anticancer drugs that associate anti-invasive therapy and cytotoxicity. Bumetanide (Bum) is a NKCC1 sodium-potassium-chloride cotransporter inhibitor that restores brain inhibition & blocks hyperactivity. Mebendazole (Meb), is a repositioned anti-helminthic drug with vincristine-like cytotoxic effects that attenuates Glioblastoma in human and experimental animals. The combo efficiently reduced migration and produced massive neuronal apoptosis in our preclinical study.

Here, we report the results of a compassionate pilot case performed in an inoperable brain metastatic breast cancer patient after failure of radio-chemotherapy, Herceptin and approved targeted therapies. The patient received 1mg/day and Meb at 200 mg three time a day without any side effect. The combo rapidly reduced cortico-therapy, tumor size, motor deficit and diplopia during the 7 months of treatment.

A rigorous trial is mandatory to progress: Our trial will associate Bum at in newly diagnosis pharmaco-resistant glioblastomas, invasive meningiomas and brain metastasis. This may pave the way for the first anti-invasive tumor microenvironmental modulating therapy in oncology, supporting a major new pharmaceutical market.

Keywords: Brain Tumors; Mebendazole & Bumetanide; NKCC1; Microtubules

Introduction

Glioblastoma remains uncurable with a 15-month median survival. Many progresses were observed in the field of multimodal imaging (including radiomics using artificial intelligence), robotic, interventional technologies and radiotherapy. Moreover, deep deciphering of molecular and cellular pathways was done using next generation sequencing and more recently single cell analysis. Despite this incredible number of innovations and data, we are still failing. Standard glioblastoma therapy associate surgery, radio-chemotherapy (temozolomide) and more recently high frequency cranial stimulation (Tissue Treating Field, TTF) [1]. Most targeted therapy trials failed [2]. Recently some responses were observed using ARN or CART-Cell immunotherapies [3], but we are still facing relapses and inability to fully neutralize local immunosuppression. Main bottlenecks for the cure are glioblastoma heterogeneity/plasticity, extensive interactions with the neuronal environment [4-6] and our inability to target the peritumoral brain. Extensive observations suggest the presence of extensive synaptic interactions between the tumors and cortical

environment and hyperactivity that is generated and enhances metastasis [7-9]. At the periphery of the tumor removed by the neurosurgeon, peritumoral cells, being proliferating, dormant or invading/migrating will pave the way for therapy resistance and relapse. A subpopulation of GBM cells harbor neuronal differentiation, migrate as neuroblast and establish synapses with these peritumoral neurons. Clearly, in addition to killing tumor cells, we need treatment that prevent metastasis by reducing neuronal hyperactivity.

Several drugs have been shown to kill tumor cells [2, 10]. Microtubule acting drugs -including Mebendazole (Meb) - are top scoring drugs to treat brain tumors according to the NCI-DTP COM¬PARE program of the National Cancer Institute (https://dtp.cancer.gov/databases_tools/compare.htm). In experimental conditions, Meb and related agents have been shown to kill cells in brain tumors in experimental conditions [11-13]. In a phase 1 clinical trial, Meb had small effects on the median overall survival [14]. Clearly, Meb is a good candidate to produce cell death in tumors.

In contrast, anti-invasive efficient drugs are not available. The sodium-potassium-chloride co-transporter NKCC1 has high translational interest for GBM therapy. NKCC1 is expressed on tumor cells and brain microenvironment actors including astrocytes and microglial cells [15-16]. NKCC1 hyperexpression in GBM is correlated with glioma grade and realizes a prognosis biomarker in aggressive mesenchymal GBM [17] and is expressed in meningiomas. NKCC1 regulates invasion and migration through its expression at the lamellipodium level and cell size regulation [18]. It also regulates MMP expression, mesenchymal aggressive phenotype, cytoskeletal dynamic that are multilevel actors for invasion/migration. The highly specific NKCC1 inhibitor bumetanide (Bum) restores GABAergic inhibition and block hyperactivity and seizures and has been shown to efficiently attenuate brain tumors [16, 19]. Interestingly, high (Cl^-) i levels and paradoxical GABA excitatory actions are present in developing neurons but also in a wide range of pathological conditions including cancers many disorders [20]. Recent evidence suggests that tumor cell subpopulations share a lot of features with immature neurons further stressing the importance of GABA polarity shift dysfunction [21]. Bum has been used in many experimental conditions and in clinical trials to treat epilepsy, autism or neurodegenerative diseases [22-25]. Clearly, NKCC1 inhibition is a major opportunity to target, the protumor neuro-glioblastoma amplification loop, targeting the migrating tumor cells and the neuronal activators (Figure 1). Here, we report a case report in which we used a combo of 2 anticancer agents to treat brain tumors, Mebendazole and Bumetanide. Early compassionate testing is important before the initiation of phase 1 to 3 trials. It provides the opportunity to detect in a non-statistical but clinical way potential side effects and patient's acceptance.

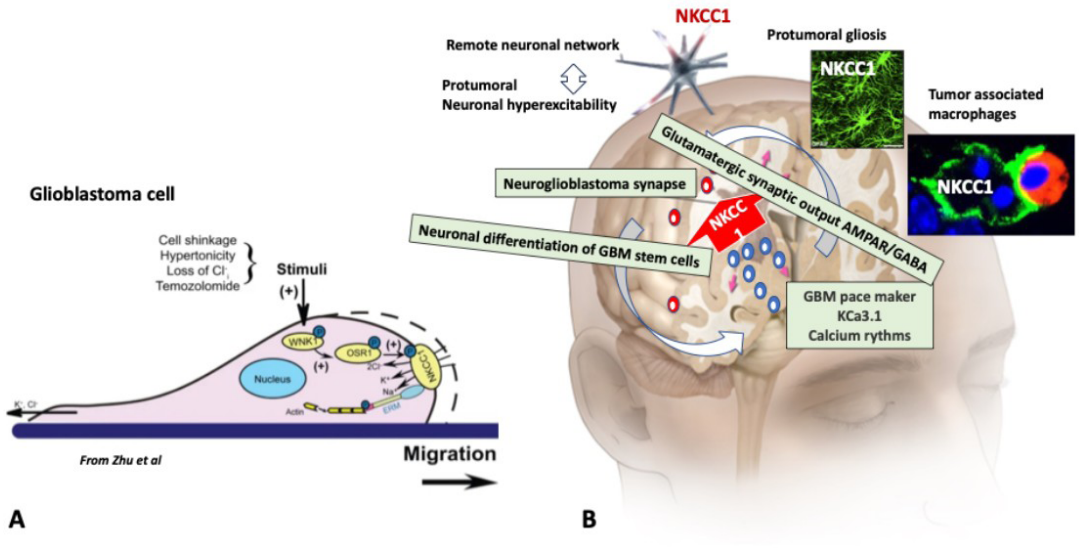

Figure 1: NKCC1: a multimodal target for GBM therapy: from "*gliomacentric*" to "*neuro-glioblastoma networks*" modulating therapy.

Material and Methods

1 patient was treated with BUM alone and another with the combo BUM+MEB as a compassionate trial once all classical treatments had failed (radiotherapy and chemotherapy with TMZ).

Results

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(Case 1) We first tested bumetanide alone in one relapsing right temporal glioblastoma patient starting at 3 mg a day using a titration strategy as done in Parkinson's disease [26]. Headaches quickly improved followed in 2 weeks by an improvement of hemiplegia (from 2 to 3 motor quantification). Bum was prescribed at 1 mg because of the non-acceptance of diuretic polyuria at 3 and 2 mg. At 2 months brain magnetic resonance imaging (MRI) was stabilized. At 5 months, relapse was observed.

(Case 2) This prompt us to rethink the therapeutically strategy. Early and fast improvement may be explained by the anti-oedema impact of Bum [27, 28] and the delayed effect by its direct anti-tumoral impact. However, a single anti-invasive agent strategy is questionable consequently to GBM plasticity and the possible switch to proliferation when invasive/migrating treatment is stopped. Therefore, the best combination is to associate the anti-invasive drug with a cytotoxic drug, even more so in highly aggressive relapsing glioblastoma. We therefore combined Bum with Meb that has demonstrated in-vivo and in-vitro effectiveness against glioma models [11, 29]. Moreover, beside the cytotoxic effect interesting modulation of autophagy, migration, immune reprogramming has also been reported. Safety was validated at high dose, in phase 1/2 trials in GBM, pediatric glioma and meningioma [14]. Safe associations to temozolomide radiotherapy, lomustine or Bevacizumab were also validated. From 10 to 100 mg/kg, it is nontoxic and well tolerated [30, 31].

Compassionate testing was done in a 35-year breast cancer brain metastatic patient (right fronto-basal and left cerebellar). This patient was previously treated by radio-chemotherapy, Herceptin and many approved targeted therapies. Bum was prescribed at 1 mg a day & Meb at 200 mg, three times a day. Patient had right hemiparesis (grade 3), diplopia, headaches resisting to 100 mg of methylprednisolone corticosteroids. Similarly to the first patients, headaches decreased quickly. In 2 weeks, motor deficit and diplopia very significantly decreased making back autonomous mobility at home. No hematological nor hepatic toxicity was reported. MRI done 2 months after the initiation of the Bum/Bem combination demonstrated a significative reduction of the tumor volume (Figure 2). Positive clinical response was maintained for 7 months. We stopped therapy at 8 months, warranting side effects. Symptoms recured and the metastatic disease progressed. Palliative cares were initiated, and the patient died 3 months later.

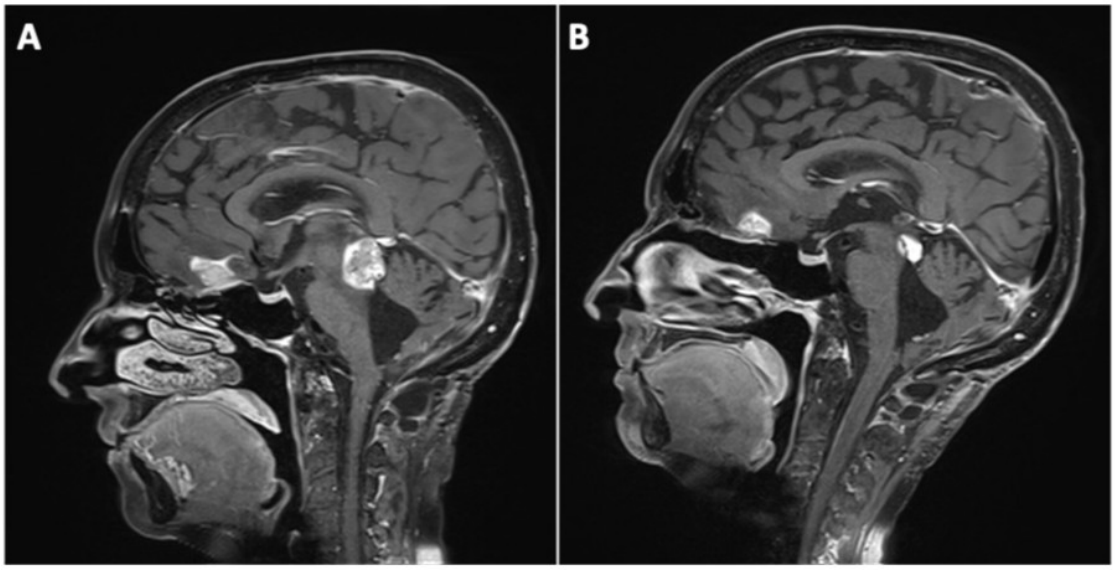

Figure 2: Breast cancer metastasis in the brain stem treated by Bum/Meb combination. MRI **A)** before therapy, **B)** at 2 months after therapy.

Discussion

We have validated at the preclinical level the synergistic impact of Bum/Meb in glioblastoma models, especially demonstrating efficacy and synergy in human tumoroid models, now the more relevant models for human glioblastoma (Bourgeois et al in preparation). Relying on these and a vast series of experimental studies we tested the rationale of combining an apoptotic agent and an anti-invasive drug that also efficiently blocks neuronal hyperactivity. The pilot case suggests that the combo produced little side effects and promising effects on attenuating deleterious events associated with the tumor as well as a significant reduction of tumor size.

We have designed a clinical trial associating Bum/Meb (Cytotoxic, Anti-invasive and anti- Neuroglioma networks strategy: BM-CAN trial). This trial is a phase I multi-center trial, associating Bum 1mg each day with Meb 200 mg three time daily. It is initiated before surgery in patients with putative glioblastoma. Rational of pre-surgery intervention is to potentially neutralize the pro-invasive effect of surgery. Patients will receive Bum/Bem combination during radiotherapy and chemotherapy. This will be maintained until progression. Objective is to validate safety of this combination associated to classical temozolomide-radiotherapy-TTF regimen. Beside newly diagnosed GBM, BM combination will be also tested in invasive meningioma and brain metastasis resisting to classical therapy.

Limitations of our study include the differences between the 2 patients and treatments. This however results from the fact that we had to first test Bum, as this has not been tested on patients with Brain tumors before. Also, the intrinsic heterogeneity of brain tumors precludes generalizing results from metastasis to other types of brain tumors, requiring therefore larger and more representative trials.

Conclusion

Despite their limitations, present results are promising in showing that the combination of these 2 generic drugs does not add novel side effects resulting from the combination, a condition for their use in larger trials. Bum/Mem combo is unique and patented by B&A Oncomedical (PCT/EP2023/071102). We trust that combination of drugs producing cell death and blocking hyperactivity to also prevent metastasis are mandatory to efficiently treat brain tumors. Our results might pave the way for an anti-invasive tumor micro environmental modulating therapy, also supporting a major unmet therapeutic need.

Acknowledgments

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Ethical guidelines

The trial was approved by the Hospital ethical committee and by the 2 patients.

Conflict of interests

FB has no conflict of interest.

Y B-A is the CEO and shareholder of Ba-Oncomedical but is not paid by the startup.

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