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CORRESPONDENCE

Metformin plus temozolomide-based chemotherapy as adjuvant treatment for WHO grade III and IV malignant gliomas

We greatly appreciated the paper by Soritau et al. "Metformin plus temozolomide-based chemotherapy as adjuvant treatment for WHO grade III and IV malignant gliomas" that has recently appeared in J BUON evidencing the *in vitro* anticancer activity of metformin on brain tumor cells [1].

In the last years metformin, an old oral hypoglycemic drug for the treatment of type 2 diabetes, claimed attention for its preventive anticancer properties and therapeutic activity against neoplasms. This activity probably relies on different mechanisms like reduction of insulin levels that could be important for prevention and, possibly, for treatment of cancers (e.g. breast and colon) associated with hyperinsulinemia [2], and interference with the LKB1/AMPK/mTOR signalling pathway [3]. In particular, mammalian target of rapamycin (mTOR), representing a target for the design of anticancer agents, is a kinase acting as a master switch between catabolic and anabolic metabolism [4].

Observational retrospective studies reported a remarkable and highly significant lower incidence of cancer in metformin-treated diabetic patients when compared with either diabetic patients on other therapies or subjects of the general population [5]. Besides these important observations that suggest intriguing insights, a growing number of clinical studies are testifying both a more favorable clinical course and a prolonged survival when adding metformin to standard chemotherapy in a large variety of cancers.

It is known that cancer stem-like cells not only are present in tumors (stem cell theory of carcinogenesis) but also play an important role in their radio- and chemoresistance. In glioblastoma cell line A172, the inhibition of mTOR by rapamycin was found to reduce the expression of neural stem cell progenitor markers and increase the expression of the neural differentiation marker βIII-tubulin. Such findings indicate that the mTOR signalling pathway plays a fundamental role in glioblastoma cancer stem-like cells biology being involved in glioblastomas' resistance to treatments [6].

As acting on the LKB1/AMPK/mTOR signaling pathway, metformin emerges as a very promising candidate to enter the panel of glioblastoma drug therapy. It is also hoped that, considering the acquired in-depth definition of the pharmacodynamic, pharmacokinetic and clinical profiles of such an old drug, that clinical trials might be easily accomplished.

In our opinion the study of Soritau et al. discloses new and very important perspectives in glioblastomas' medical therapy. This is especially noteworthy since in glioblastoma patients the actual standard therapy gets only scant results and, consequently, the prognosis is extremely poor and the survival is usually very short. The Soritau's group offered the basic experimental evidence to allow incorporation of metformin as a new, safe, cheap and favorable tool in the therapy of gliomas. Prospective *in vivo* studies will precisely assess the clinical efficacy of metformin in the therapy of high-grade gliomas.

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Reply to Dr. Valle et al.

When Professor Vladimir Dilman's research team at the Petrov Institute of Oncology in St. Petersburg first published in the 1980s the concept that antidiabetic biguanide drugs can act as promising anticancer pills and genoprotectors, the idea of metabolic rehabilitation was not as appreciated as it might be in the near future [1]. Things changed when epidemiology data has shown that metformin significantly reduces cancer incidence and improves the long-term survival of patients previously diagnosed with breast cancer, suffering also from type 2 diabetes. Metformin may act in the neoadjuvant setting by physically combining the long-lasting effects of a persistent low level of blood insulin and glucose. Furthermore, it may enhance the antineoplastic effect of a cancer cell-targeted molecular agent by suppressing the pivotal AMPK/mTOR/S6K1 axis and with it, of several other protein kinases including tyrosine kinase receptors such as HER1 or HER2 [2]. This solves some of the questions raised last year at the Annual Meeting of the American Society of Clinical Oncology on breast cancer chemotherapy. The activation of the mammalian target of rapamycin (mTOR) has also been proven to induce differentiation of embryonic stem cells [3]. As a small population of cancer cells has been proven to have stem-like properties, it would be fair to assume that mTOR activation by metformin may differentiate the cancer stem cell niche in malignant gliomas, turning it into a much more sensitive target for temozolomide, as proven by our study [4]. Differentiation of the stem cell compartment in the

subventricular area of the adult brain, may it be either normal or cancerous, will not affect the normal tissue physiology as they have differential sensitivity to chemotherapy, as proven by the team of Bota et al. in the US [5].

This old drug may actually work even better in comparison with drugs developed by cutting edge research, as it is readily available, very inexpensive and very well tolerated by the human body, having very little or no side-effects. The data is supported by international efforts to introduce metformin in the standard-of-care of various solid malignancies. Such is the case of the European Institute of Oncology in Milano, that is currently planning a pre-surgical randomized double-blind, placebo-controlled phase II biomarker trial for breast cancer not suitable for neoadjuvant therapy that will be assigned to either metformin (850 mg twice/daily) or placebo tablets until surgical resection [6]. The real activity on tumor proliferation as measured by Ki-67 staining will be assessed. Still, even if the introduction of biguanides in malignant glioma therapy is still not possible, this alternative raises a lot of questions that can only be solved by further, more detailed *in vivo* studies in animal models.

References

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