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LETTERS TO THE EDITOR

Possible role for furazolidone in the treatment of glioblastoma multiforme

Dear Editor,

The process of finding new uses of existing drugs outside the scope of the original indication is referred to as repositioning. Nowadays, more and more pharmaceutical companies are exploring the existing pharmacopoeia for repositioning candidates, especially for diseases where current therapy is ineffective. Glioblastoma multiforme (GBM) is such a case representing the most common and most aggressive malignant primary brain tumor in adults.

Despite maximal treatment, consisting of surgical resection followed by radiotherapy and temozolomide (TMZ) chemotherapy, GBM relapse occurs regularly, accompanied by unfavorable prognosis. The presumed cause of GBM recurrence is a sub-population of tumor stem cells (TSCs) which has been shown to be resistant to standard therapy. GBM shows a sub-population of TSCs that overexpress aldehyde dehydrogenase 1A1 (ALDH1A1), a cytoplasmic isoform of ALDH, which is considered to be a stem cell marker in human GBM. High levels of ALDH1A1 in established GBM cell lines seem to keep tumor cells in an undifferentiated state while in contrast ALDH1A1 inhibition induces premature cellular differentiation. In addition, ALDH1A1 has been shown to be a mediator for resistance of GBM to TMZ and a reliable predictor of clinical outcome with better prognosis for GBM patients with low ALDH1A1 levels. Consequently, ALDH1A1 may serve as a potential target to improve treatment of human GBM through inhibition of the enzyme.

During the course of a research project in our laboratory, we investigated all known ALDH inhibitors in the Wistar rat and we concluded that among these inhibitors disulfiram (DSF), a relatively nontoxic pharmaceutical agent used for more than 60 years in the treatment of alcoholism, possesses the strongest inhibitory effect on ALDH1A1 [1]. In a position paper based on our experimental work it was hypothesized that DSF, through inhibition of TSCs ALDH, might be of importance in the treatment of GBM by making TSCs less able to regenerate a stem cell derived tumor mass after primary therapy [2]. This was actually the first report in the literature regarding a possible implication of DSF in GBM treatment. Such a role for DSF was later supported by a number of in vitro studies where DSF was shown to be cytotoxic on human GBM cell lines and ALDH-positive TSCs overriding the resistance of GBM to TMZ through multiple mechanisms (including ALDH inhibition) [3-5]. Based on these results two clinical trials testing DSF in GBM patients are about to commence (NCT01777919 and NCT01907165; the former organized by our Institute).

Furazolidone (FUR) is one of the synthetic antimicrobial nitrofurans used nowadays mainly in countries with low socioeconomic levels for the treatment of diarrhoea or enteritis caused by bacteria. It may also be useful in treating traveller's diarrhoea, typhoid fever, cholera, salmonella infections and H. Pylori-related peptic ulcers. In addition, we showed that FUR is the second strongest inhibitor of ALDH1A1 after DSF [1]. Likewise, we could hypothesize that as in the case with DSF, FUR could probably inhibit TSCs ALDH1A1 of GBM patients with the potential to reduce the recurrence rate of the tumor. Moreover, FUR is an inexpensive and easily administered drug, but most importantly it is able to cross the blood-brain barrier, which is a major limitation in brain therapeutic design. Consequently, we believe that FUR has the potential to be tested as adjunct in GBM chemotherapy. Since this drug is well established with extensive safety data available it would be possible to go directly into a phase II study to establish the potential place of the product in the treatment of GBM.

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Dissociated evolution of a multifocal primary CNS lymphoma

Dear Editor,

Primary central nervous system lymphoma (PCNSL) is a rare presentation, usually as a diffuse large B cell lymphoma (DLBCL), and is a hardly curable malignancy with high relapse risk. We describe here in the case of a patient with a very unusual evolution of a PCNSL.

A 56-year-old male patient presented with left facial palsy and rapid evolution to left hemiparesis. Brain MRI showed the presence of two lesions situated one in the left temporal lobe and the second, contralateral, in the right Rollandic region. A biopsy of the temporal lesion was performed and showed massive infiltration of the cerebral tissue by large cells disposed along the vessels, with frequent mitoses. Immunophenotyping showed lymphocytes positive for CD20 and CD19 and negative for ALC, CD45, CD3, CD5, and CD30 establishing the diagnosis of DLBCL. No other localization was found on CT scan or 18 F-FDG PET scan. Cerebrospinal fluid cytology was negative. The patient was treated using the GOELAMS CNS MBVP (high dose methotrexate, carmustine, etoposide and methylprednisolone) induction protocol for 4 cycles, followed by 2 cycles of consolidation therapy with ifosfamide and cytarabine. After induction therapy, follow-up MRI showed complete remission of the initial lesions, but the presence of a new small lesion in the deep left parietal lobe. After two cycles of consolidation chemotherapy, the patient developed Broca's aphasia, with loss of verbal expression and profound impairment of mnestic functions. A new MRI found a very unusual evolution of the cerebral lesions, with persistent responses of the left and right temporal lesions, and an evolution of the new, left parietal lesion. A new biopsy was performed, confirming lymphoma with the same histological characteristics as at diagnosis. A rescue therapy using ESAP (etoposide, cytarabine, methylprednisolone and cisplatin) associated with rituximab was started. After two cycles of chemotherapy, the patient showed complete clinical recovery. MRI found an important regression of the left parietal lesion, with residual oedema. The patient was scheduled for intensive chemotherapy followed by autologous stem cell transplantation.

Representing approximately 1-2% of all cases of non-Hodgkin's lymphoma, PCNSL is a rare disease affecting patients with a median age of over 60 [1]. Although in almost 90% of the DLBCL cases, response to chemotherapy as well as protein and gene expression patterns of PCNSL and systemic DLBCL differ [2]. Treatment of PCNSL is still a challenge and results are difficult to interpret because of the low occurrence of this type of lymphoma. Standard regimens are based on high dose methotrexate [3] followed by whole brain radiotherapy. It has been proven that the initially impaired blood–brain barrier is restored within 4–6 weeks of therapy, impending CNS penetration of multiple chemotherapy agents. In a recent phase 2 study Ferreri et al. reported that the association of high dose cytarabine to methotrexate improved the overall response and overall survival [4]. It has been proven that high dose chemotherapy followed by autologous stem cell transplantation is an interesting option in patients with cerebral lymphoma [5]. Relapses are frequent and their management difficult because of the low numbers of drugs passing the blood–brain barrier, and/or because of patients' co-morbidities.

In our patient, a "classical" treatment including high dose methotrexate, obtained remission of the lesions present at diagnosis, but a new lesion developed and evolved under consolidation chemotherapy, with the same histological characteristics as at diagnosis. The lesion responded to platin-based rescue chemotherapy. To our knowledge this is the first reported case of a dissociated evolution of a PCNSL, and could represent a case of resistant clone selection under chemotherapy.

Disclosures

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Correlation of serum proteomics patterns of sCD200 (OX-2), sApo-2L (sTRAIL), vitamin-D and homocysteine to quantitative FDG-PET/CT findings in newly diagnosed non-small cell lung cancer

Dear Editor,

Trends in lung cancer incidence and mortality reflect smoking habits and/or exposure to other environmental or occupational carcinogens [1]. Although it has been shown that TRAIL can activate both pro-apoptotic and anti-apoptotic pathways, the reasons for directing to one or the other of these pathways are not completely understood. In our previous study we were able to show that sTRAIL (sApo-2L) levels are significantly higher in newly diagnosed metastatic non-small cell lung cancer (mNSCLC) than in healthy controls [2].

1,25- dihydroxyvitamin D(3) (Vit-D) is a steroid hormone that is now widely accepted to exert several extraskeletal actions, including antitumorigenic and immunomodulatory effects in vitro as well as in vivo. In relation to the lung, evidence from observational studies, animal models and in vitro cell culture suggest that Vit-D may play a beneficial role in pulmonary inflammation [3]. Gene promoter hypermethylation is now regarded as a promising biomarker for the risk and progression of lung cancer [4].

Positron emission tomography and computed tomography (PET/CT) with F-18-deoxyglucose (FDG), a glucose analogue, is an advanced imaging technique and supports a highly sensitive whole body search for malignant foci, which are detected due to their increased glucose metabolism vs benign tissues. Successful scanning has been performed in a wide variety of cancers [5]. Regarding more effective therapeutic options for advanced disease stages the current follow-up procedures for lung cancer are insufficient. Therefore, in the present study, we investigated the concentrations of sTRAIL, Vit-D, homocysteine (Hcy), and sCD200 in the peripheral blood of patients with newly diagnosed metastatic squamous cell lung cancer (mSCLC) not receiving chemotherapy. Furthermore, the corresponding FDG PET/CT results were evaluated.

We measured these parameters in the serum of 22 patients with mNSCLC. The patients were scheduled for chemoradiotherapy with two cycles of 50 mg oral etoposide per week, continuously, and i.v. cisplatin at 4-week intervals; no surgical resection or radiation therapy were performed. Prior to chemotherapy, whole-body FDG PET/CT was performed using a Philips GEMINI GXL6 camera. Tumor volumes were determined by using an interactive, semiautomated method. Serum samples were obtained prior to chemotherapy. ELISA was performed using the Diaclone sTRAIL ELISA kit (Gen-Probe, Besancon, France) and Roche kit for Vit-D and Hcy and the processing was done according to the manufacturer's instructions. The absorbance of each probe was measured with a spectrophotometer using 450 nm and the concentrations of sApo-2L (pg/mL), Vit-D (ng/mL), Hcy (mmol/L) and sCD200 (pg/mL) were calculated from standard curves.

The study population comprised 19 of 22 patients with mSCLC, who underwent PET/CT scanning prior to treatment.

We used the ln (SUVmax) for all calculations. Correlation analysis revealed a significant correlation for the SUVmax as well as the ln (SUVmax) in the primary tumor prior to treatment (survival and SUVmax: r=-0.5691, p=0.0268, N=15; survival and ln (SUVmax): r=-0.6954, p=0.0040) (Figure 1). The results demonstrated that about 50 % (100*0.6954*0.6954) of the variation of the FDG kinetics are explained by an existing correlation between these two variables (Figure 1). Furthermore, we also calculated a multiple linear regression function using the PET and laboratory results. For this purpose a t-value < 1 was used to select those variables significant for the multiple linear regression analysis. The results revealed that the overall survival correlated with r=0.7886 (p=0.0720) with ln (SUVmax), sApo-2L, Vit-D, Hcy, and sCD200. Thus, the explained variance of the FDG kinetics could be enhanced to about 62 % .

In conclusion, F18-FDG uptake on PET scan is an independent prognostic predictor in mSCLC patients. The present study indicates that the determination of SUVmax is an effective non-invasive method for newly diagnosed stage 4 mSCLC patients, and is useful in developing strategies for individually adapted treatment. The combination of serum measurements plus the quantitative PET/CT results revealed the best correlation with survival and may help to perform individualization of therapy.

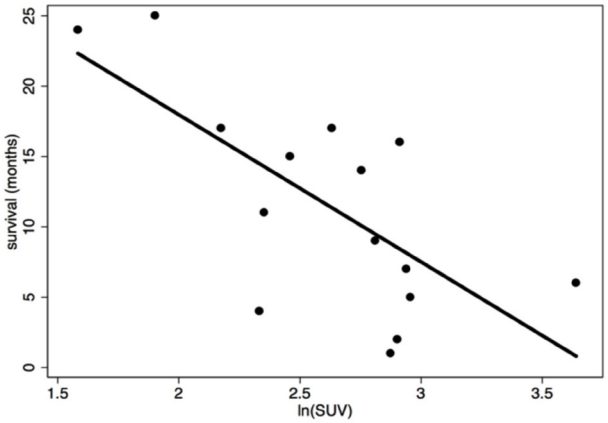

Figure 1. Correlation analysis reveals a significant correlation for the SUVmax as well as the ln (SUVmax) in the primary tumor prior to treatment (survival and SUVmax: p=0.0268; survival and ln (SUVmax): p=0.0040 (r=-0.6954, N=15).

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