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Abstracts

Neuroncology

RADIOTHERAPY AND TEMOZOLOMIDE IN GLIOBLASTOMA: PREDICTIVE FACTORS OF RESPONSE TO THE TREATMENT

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Despite the efforts to improve the standard treatment [surgery, radiotherapy (RT) and chemotherapy], at present, the median survival of patients with glioblastoma (GBM) is poor and almost of patients die for local recurrence. In 2005, the trial of EORTC/NCIC[1] have established what the treatment with concomitant temozolamide (TMZ) and RT (plus adjuvant TMZ) has increased the overall survival since 10% (after the RTalone) to the 26% (after combined treatment). This benefit however is not reached in all the patients, because of the presence of molecular abnormality among the patients and also inside the same patient. The aetiology of GBM is unknown, and' is brought that at least two genetic pathways is implicated in its development: primary (*de novo*) and secondary glioblastoma. Temozolamide is a new alkylant agent, orally active, derived from dacarbazine with proven efficacy in the treatment of GBM. Hegi et al.[2] have reported what the mechanism of action of the TMZ resides in the alkylation of the DNA (position O6 of the guanine): such damage comes in the normally by the O6-methyl guanine-DNA methyl transferase (MGMT) (Fig. 1).

The MGMT is implicated in the tumoural resistance since it is partially able invalidate the effect of the alkylant agents on the O6 guanine. The study of Hegi et al.[3] has brought that the patients, treated with TMZ+RT in which the promoting gene of the MGMT is methylated they show a median survival (at 2 years) of 46%, in comparison to those essays with RT alone, for which instead the survival is of 23%. In the patients that introduce the promoter gene unmethylated they show a survival, at 2 years, after treatment with TMZ + RT, of 14%. Chakravarti et al.[4] in the 2006, using a panel of four primary human glioblastoma cells, reported that TMZ '*enhances radiation response most effectively in MGMT-negative glioblastomas by increasing the degree of radiation-induced double-strand DNA damage. In MGMT-positive glioblastomas, depletion of MGMT by the addition of the O(6)-benzylguanine significantly enhances the antitumour effect of concurrent radiation+ temozolamide.*'

Additionally, Sarkaria et al.[5] studying a panel of GBM orthotopic xenograft, have reported that the treatment with TMZ did not sensitize tumours presenting MGMT unmethylated to radiation, but the treatment with TMZ appears to sensitize MGMT-methylated tumours to radiation.

Moreover, the temozolamide expounds also its function alkylant in the respects of the position N-7 of the guanine and the

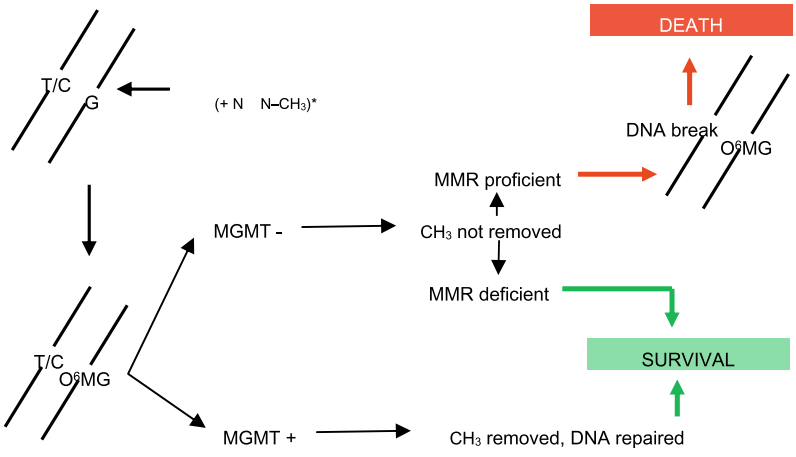

Fig. 1. Image reported from Metha MP, X Congresso Nazionale e Corso Residenziale dell'Associazione Italiana di Neuro-Oncologia, Napoli 7–9 Novembre 2005.

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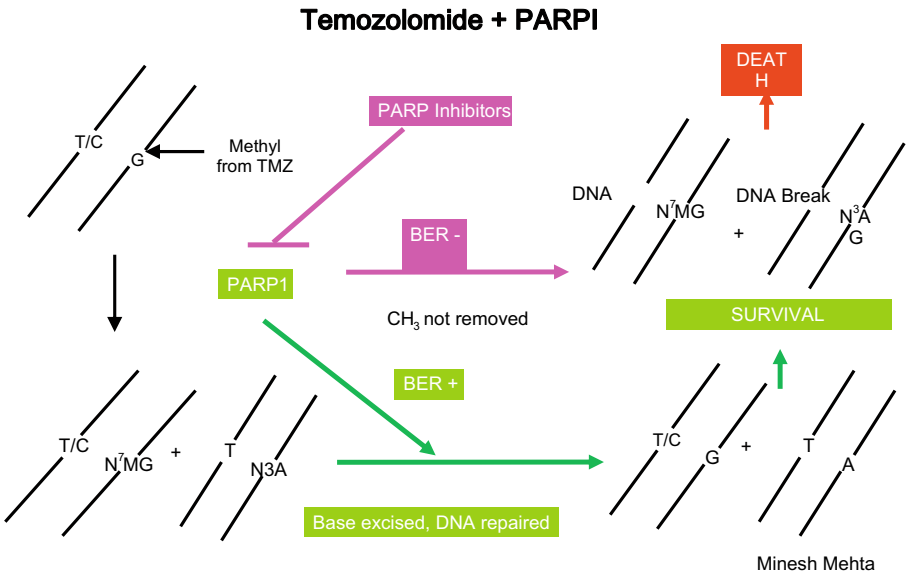

Fig. 2. Image reported from Metha MP, X Congresso Nazionale e Corso Residenziale dell'Associazione Italiana di Neuro-Oncologia, Napoli 7–9 Novembre 2005.

position N-3 of the adenine, whose damages are mended then by enzymes of the family of the PARP. The latter two are repaired by enzymes in the base excision pathway, which can be inhibited by PARP inhibitors (Fig. 2).

At present, are ongoing clinical trials using MGMT or PARP inhibitors to overcome the TMZ resistance.[6]

The TMZ, in preclinical data, shows an additive effect with the radiation.[7]

In conclusion, in the treatment of glioblastoma, further studies are need to the purpose to integrate basic research and clinical practice.

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CONTRIBUTION OF THE FUNCTIONAL IMAGING IN THE RADIOTHERAPY TREATMENT PLANNING FOR MALIGNANT GLIOMA: REVISION OF THE LITERATURE

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Currently, despite the efforts to improve the standard treatment [surgery, radiotherapy (RT) and chemotherapy], the median survival of patients with glioblastoma (GBM) is poor and almost of patients die for local recurrence, both to the inside and to the outside of the tumoural bed. In consideration of the disappointing gotten results, the question that emerges if it is possible to improve radiotherapy planning integrating of new imaging techniques. To the moment the standard is the use of the imaging CT and Magnetic Resonance Imaging (MRI)-based, but for instance MRI is not able to differentiate residual tumour and post-operating modifications. In addition to the anatomic and morphological findings available with con conventional imaging methods, advanced MRI and Nuclear Medicine (NM) techniques can give information on the metabolism of malignant glioma cells. In this study we have analysed the following methodic of functional imaging: 123I-alpha-methil-tyrosine-single photon emission CT (IMT-SPECT), single-voxel proton magnetic resonance spectroscopy (1H-MRS), functional MRI, diffusion tensor imaging (DFI), [F-18]-fluorodeoxyglucose positron tomography (18FDG-PET) and L-(methyl-11C)-labelled methionine positron emissions tomography (MET-PET), to the purpose to integrate her in the target delineation and in radiation dose escalation. Every of the new techniques show potentiality and limits. For instance, in comparison with 1H-MRS, 123I-IMT-SPECT introduces best results in to distinguish amongst recurrent and/or residual tumour from the post-operative changes and can be useful in the definition of the volume target with greater accuracy and in consideration of '*the high specificity of the IMT uptake for the tumour tissue, the findings on IMT-SPECT may significantly modify the target volumes for radiotherapy planning. This will help to focus the high irradiation dose on the tumour area and to spare normal brain tissue*'.[1] The 1H-MRSI showing a high specificity and sensibility in to distinguish between therapy-related effects and relapse, it finds her application in the assessment of probability of response or failure to the treatment. Since, radiation dose escalation in malignant glioma may lead to an increase of the disease control, the 18FDG-PET may be of great utility in to define the regions for which to plan to radiation dose boost. The assessment of diffusion properties may add information, during the follow-up, in to distinguish between recurrence and radiation effects. In post-