THE NEED TO ACHIVE A MULTIMODAL THERAPEUTICAL APPROACH IN GLIOBLASTOMA

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ABSTRACT

It is well-known that of all the brain gliomas the glioblastoma multiforme has always caused serious difficulties regarding its therapeutic solution by means of different methods. Glioblastoma multiforme is the most frequent primary brain tumor in adults. The average survival time after the establishment of the diagnosis varies between 12 and 14 months and less than 5% of the patients survive for longer than five years. Despite the progresses recorded in the identification of the complex biology of these tumors, the prognosis has not been substantially improved over the last three decades. Therefore an important attention has to be paid to the continuous review of the therapy of this disease (surgical treatment, radiotherapy and chemotherapy),a special place belonging to the administration of temozolomide, as well as the cell- and gene therapies.

Key words: glioblastoma, multimodal therapy, gene therapy, temozolomide, cell therapy

Gliomas as a whole constitute the best represented category of primary brain tumors in the intracranial tumoral pathology. Among them the cerebral glioblastoma (fig.1,2,3) is a totally special anatomo-pathological and clinical entity with particular histo-pathological and evolutive characteristics, requiring specific therapeutical approaches in order to improve the very severe evolutive prog-

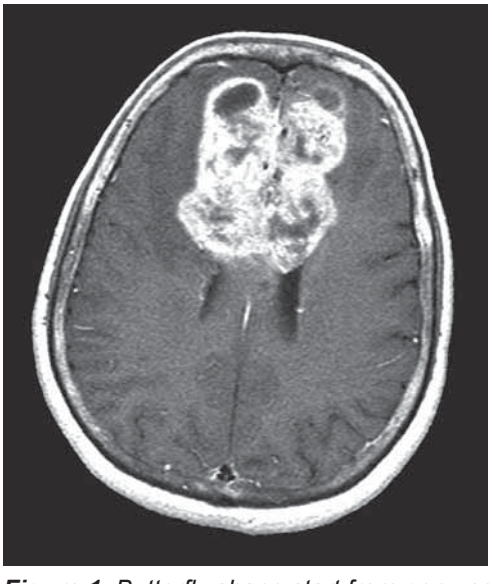

Figure 1. *Butterfly shape start from genu corporis callosi and bifrontal invasion*

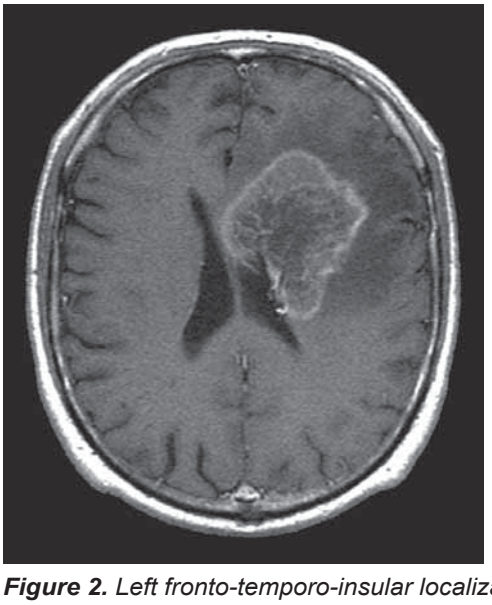

Figure 2. *Left fronto-temporo-insular localization*

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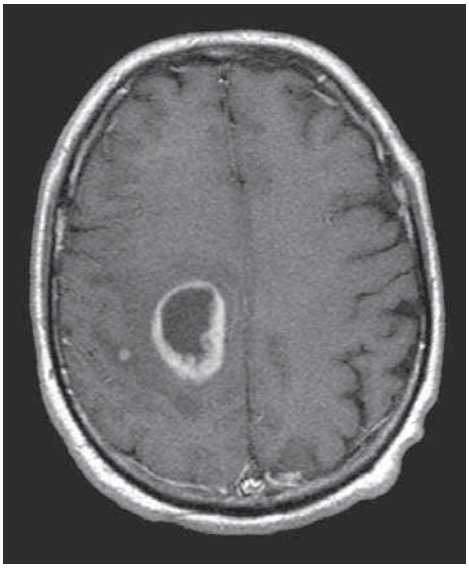

Figure 3. *Right deep frontal paramedian localization.We are remarking marginal gadolinium enhancement and central necrosis zone.*

nosis of this malady. The international results in the fight against this disease impose a more intensive search for new therapeutical methods for the improvement of the postsurgical prognosis of the glioblastoma multiforme.

MRI aspects- secquence T1, of various localizations of glioblastomas are shown in the next pictures.

Thence, glioblastoma multiforme is the most frequent primary brain tumor in adults. The average survival time after the establishment of the diagnosis varies between 12 and 14 months and less than 5% of the patients survive for longer than five years. The primary brain tumors affect a considerable segment of the population, their incidence being estimated according to the last statistics to over 10 /100.000 individuals /year (CBTRUS, 2005). More than 50% of the primary brain tumors are brain gliomas and among these tumor lesions the glioblastoma represents the most frequent form (approximately 60% of the total number of gliomas) and with the most severe prognostic. They may appear in any region of the central nervous system and in any age, but the most frequent site is the white matter of the brain hemispheres and its incidence is most common in the age groups between the 5th and 6th decade of life. Concerning the particular localizations of glioblastomas, it is worth mentioning those starting from corpus callous and the basal ganglia level, as well as those at the spinal cord level (encountered both in adults and in children) and from the level of the brain stem (situation encountered among children), the last two representing unfrequent cases in the medical practice (Greenberg, 2006).

Despite the progresses recorded in the identification of the complex biology of these tumors, the prognosis has not been substantially improved over the last three decades. The failure of the different therapy schemes can be explained by: the intrathecal localization of the tumors, which impedes the effect of some drugs that are not able to penetrate the blood- brain barrier, the instability of the gene structure of the glioblastoma tumor cells, which gradually leads to chemoresistance, while the lymphocytes that infiltrate the tumor, although they are morphologically normal, manifest a functional activation of the oncogenic routes, which contribute to fast evolution of the primary tumor and the development of metastases (Elliott et al.,2006)

Independently from any other adjuvant therapy, it is considered that the **quasi-total surgical resection** of the tumoral mass, when it is possible, improved through microsurgical techniques, remains indubitable compulsory, since it has an undisputable value for the short-term vital prognosis and the patient's neurological amelioration, as well as for the medium- and long-term prognosis, as it makes possible the subsequent administration of the complementary therapies. Of course some impediments, such as the impossibility to obtain a convenient limit of „oncologic safety" in nervous central system and the dissemination of the malignant tumor cells along the nervous pathways, considerably restrict the performance of the surgical treatment.

Radiotherapy is compulsory associated in the order to destroy the far-distance infiltraded cells of the tumor bed and to prolong the term of recurence. The relatively short survival time of the patient (the average survival time after surgery and radiotherapy is only 9 months) allows the administration of large radiation doses, as the long-term side effects of the radiotherapy usually appear after 9-12 months. Of the maximum 60-Gray dose 40 Gray are administered on the whole brain and about 15-20 Gray on the tumor (Narayana et al., 2006).

As regards the adjuvant **chemotherapy,** the alkylating agents are most frequently used, but their effect are rather small; substantial effects are obtained in only 10% of the cases. The most common of them, with similar performance, are: carmustine (BCNU), CCNU, procarbazine and cisplatine (Clarke et al., 2010). A method of increasing the efficacy of the chemotherapy could be to increase the administered dose. Because of the absence of specificity of the chemotherapeutic drugs that are currently used this would cause major systemic

side effects. Thus, attempts have been made with the intracarotidian administration of carmustine in order to increase the drugs concentration in the tumor without increasing the systemic concentration. But cerebral side effects such as leukoencephalopathy and retinal toxicity with decrease of the visual acuity appeared.

Another method to increase the local concentration of the chemotherapeutic agents without systemic increase is reprezented by the implantation of 4 to 8 polymeric capsules impregnated with carmustine at the level of the tumor resection bed during the neurosurgical intervention. These capsules slowly release the chemotherapeutic agent over 2-3 weeks and increase the concentration up to more than a hundredfold in comparison with the systemic intravenous administration of this substance. Some studies have proved an increase of 40 to 53 weeks of the average survival time for the cases of de-novo glioblastoma. Nevertheless, in the USA the application of these carmustine-impregnated capsules has been approved only for recurrent glioblastomas (Clarke et al., 2010).

One of the most promising alkylating substances with the fewest side effects is *Temozolomide*, which is especially used for the newly diagnosed glioblastoma. The action of the Temozolamide is complex and comprises the anti-tumoral, anti-angiogenetic activity and the inhibition of some signaling routes implicated the migration of the glioblastoma cells and metastasis (Clarke et al., 2009). The metastased cells which are usually radio-resistant could remain sensible to the administration of the Temozolamide. In brief, in this case the treatment should be administered as follows: adults, in association with radiotherapy (RT) and then as monotherapy (75 mg/m^2 body surface area, daily for 42 days (up to 49 days) concurrently with focal radiotherapy: 4 weeks break, followed by monotherapy with Temodal, 6 cycles of treatment: Cycle one: 150 mg/m^2 /day, 5 days, then 23 days off treatment; cycles 2-6: the dose is increased to 200mg/m^2 if the non-hematological toxicity CTC for Cycle 1 is of $\leq$ 2 degree (except for alopecia, nausea and vomits), absolute number of neutrophils (NAN) $\geq$ 1,5 x 10^9/l and number of platelets $\geq$ 100 x 10^9/l (Strupp et al., 2005)

In adults with newly diagnosticated glioblastoma multiforme the administration of Temozolamide will be definitively interrupted during the concomitant phase of radiotherapy and Temozolamide if NAN < 0,5 x 10^9/l; number of platelets < 10 x 10^9/l; non-hematological toxicity CTC (except for alopecia, nausea and vomisments) of 3rd or 4th degree. The treatment with Temodal must also be interrupted in case of: pancytopenia, co-morbidities, non-responder, therapeutic noncompliance (Strupp et al., 2005).

Despite the fact that big efforts have been made with the traditional treatment of the cerebral glioblastoma, the results are still unsatisfactory, especially because of the remarkable capacity of this type of tumor to relapse, as well as because of the big dissemination potential along the nervous system pathways. All this reasons press on to comb out new complementary therapies intended to intefere within the genetic and molecular mechanisms that have been recently detected in glioblastoma.

Among the first cell therapies developed for the experimental glioblastoma was the use of some killer lymphocytes that are non-specifically activated by exposure to cytokines and the stereotactic inoculation in the tumoral mass. These mass attempts have given disappointing results for the very reason that they effected a non-specific activation of the killer lymphocytes. The performance of the chemotherapeutic drugs used in onco-neurosurgery depends on their capacity to penetrate the hematoencephalic bar. Ambitious studies have tested the possibility to administer in CSF chemotherapeutic agents that have proved to be effective in the treatment of the leptomeningeal disease and that had no major side effects. This strategy prevents the metastases that disseminate through CFS, as well as the transcytosis of tumor cells beyond the blood-brain barrier.

Radio-chemotherapy and maintenance therapy with temozolomide (TMZm) have brought an amelioration of the prognosis for GMB. On the other hand, *gene therapy* is a very interesting alternative for the treatment of the cerebral tumors because of the absence of the systemic toxicity and the relatively simple administration through stereotactic procedures and craniotomy. Gene therapy offers the possibility to complete the conventional cancer treatment (chemoterapyc drugs, radiotherapy and surgery).

Beside molecular therapy and gene therapy, other possible therapeutic alternatives, such as the intervention of biological agents (tamoxifene, antisense oligonucleotides, protein-kinase inhibitors etc) or the intervention of antiangiogenic and cytotoxic agents (topotecan, CPT-11, temozolomide etc), must also be considered.

However, irrespective of the „promises" of these new alternative therapeutic methods, the „classic methods" in the treatment of glioblastoma, respectively surgery – as far as possible with inten-

tion of radicality, radiotherapy and chemotherapy, still have a great importance. All of them must be accordingly adapted to the individual cases (age, general and neurological condition, comorbidities, metastases), so that the whole assembly of therapeutic measures should ensure the highest possible life quality, social reintegration and long survival.

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