Malignant Brain Tumors: Death Sentence, No Mercy

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Abstract: The article presents critical analysis of current methodological approaches, the standard and the options of complex therapy of malignant brain tumors (MBT). Author defines the main reasons for low effectiveness of MBT therapy. Relying on post-genome innovations (mass-spectrometry proteome mapping and whole transcriptome profiling of gene expression of cancer cells (CCs), cancer stem cells (CSCs) and tissue-specific stem cells (TSSCs) of the cancer patient, and their comparative analysis) the author proposes systemic solution for the MBT complex therapy that consists in a new alternative paradigm of cytoregulatory anti-cancer treatment of the MBT that is aimed at rigid control, management and regulation of the number of CCs and CSCs in the body. The goal of a new treatment paradigm is to transfer acute, uncontrollable and mortal process into chronic and non-lethal disease, and, thus, to improve survival rates and life quality of the patients. The instrument to implement the new paradigm is a sparing algorithm of conventional therapeutic methods and immune therapy, supplemented with personalized anti-tumor proteome-based cell therapy. The therapy implies transfusions of transcriptome-modified autologous TSSCs with specified properties to regulate the reproductive functions of the CSCs. The author proposes the complex therapy of the MBT and shows its social and economic significance for the society and neuroscience.

Keywords: Malignant tumors of the brain, Standard and options of tumor therapy, Neurooncology, Brain cancer, Metastases to the brain, Glioblastoma multiforme, Complex anti-tumor therapy, Proteome-based cell therapy, Post-genome technologies.

INTRODUCTION

Cancer and other malignant tumors are aggressive severe somatic diseases that can injure any organs and tissues; they rate the second as the leading cause of deaths and primary disability of adult population [1]. According to IARC data 14 million of new cases of cancer are registered every year and 8.2 million of people die from cancer annually [2].

According to the American Society of Clinical Oncology, timely and correct therapy of cancer and malignant tumors increased 5 year survival of the patients by 14-19% and reduced mortality caused by cancer by 30%, due to the introduction of the therapeutic programs of early administration of new anti-cancer pharmaceuticals [3]. This significant achievement in the oncology is induced by the clinical application of the new generation of targeted anti-cancer drugs. The innovation is underlain by the fundamental advances of contemporary biology of cancer based on the genome analysis, whole transcriptome analysis of gene expression of cancer cells (CCs) and cancer stem cells (CSCs) [4-6], and on the oncoproteomic mapping and profiling of CCs and CSCs [7, 8]. Detection of a range of new oncospecific proteins in genome and post-genome assays allowed to determine new targets for the targeted therapies of cancer and to develop a whole series of innovative anti-cancer target drugs that specifically eliminate CCs and part of CSCs [9-12].

However, the expected results still has not been achieved [13-15]. Available genome and post-genome approaches of targeted anti-cancer therapy proved effective in the general oncology, but displayed low effectiveness in the therapy of malignant brain tumors (MBT). The diagnosis of MBT, as well as the metastases of cancer to the brain, remains the death sentence with no right for mercy. The median survival time of the cases of glioblastoma multiforme (GBM) varies from 12 to 15 months [11, 16, 17], and in the cases of the metastases of lung and breast cancer, the median survival time does not exceed 6-8 months [18]. Despite obvious progress in medicine in general, and in oncology in particular, these indicants remain stable for the last hundred years and do not depend on the scope of the accumulated evidence, or on the current achi-evements of cancer therapy with novel drugs [19, 20].

We believe that the time has come to revise the dominating ideas and concepts of the MBT treatment and to set the benchmarks for further research. It is necessary to determine the fundamental reasons for

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the failures and systemic errors of the MBT therapy and to critically evaluate the challenges. Obviously, the paradigm of the MBT treatment has outdated, and we have to develop a new alternative paradigm of the MBT treatment.

THE STATE OF ART AND AVAILABLE OPTIONS OF THE MBT TREATMENT

Critical analysis of the state of art in the MBT therapy and our own clinical practice showed that the efficacy of the MBT treatment is extremely low [19, 20].

Although active complex therapy does not guarantee maximal duration of life, the quality of life can be improved in many cases. The survival rate of the cases of slowly growing differentiated gliomas varies from 32 to 68% (5 years) and from 19 to 39% (10 years). For rapidly growing anaplastic astrocytomas, one year survival rate is shown by 85.5% cases, two years survival by 70.9% and three years survival by 27.3%. In glioblastoma, the 68.1% cases survive up to one year, 23.7% up to two years and 4.3% up to 3 years [14, 16, 19, 21, 22].

The truth behind these achievements is that there is no protocol, no pharmaceutical or biotechnology that can provide at least two-year survival to glioblastoma patients. Obviously, the regular army of neuroncologists, oncogeneticists, and molecular biologists is not able to cope with the MBT. It is the time to face the truth and to acknowledge that contemporary neurooncology arrived to the scientific dead end in their search for effective therapy of MBT.

THE REASONS FOR THE FAILURES IN THE MBT THERAPY AND POSSIBLE WAYS OUT OF THE CRISIS IN NEUROONCOLOGY

Our theoretical analysis of the state of the affairs in the MBT treatment showed that the main reasons for its ineffectiveness lie in the erroneous scientific methodology and absence of scientifically grounded theoretical concept of contemporary therapy of these diseases, and not in the lack of the fundamental molecular-biological and applied clinical knowledge. The evidence gathered in the sphere of molecular biology of cancer and MBT are multi-faceted and fundamental and are sufficient to develop effective medical technology [23-27]. Meanwhile, the formal barriers, standardized therapeutic dogmas and organizational prejudices are so systemic and huge that resist any alternative considerations of the methodology of the treatment of these neoplasms.

We think that one of the key reasons for the regular failures in the MBT therapy is that the neurooncologists became the hostages of the standards, regulations and guidelines of contemporary neurosurgery and neurooncology. The neurosurgeons walked away from the dogmas of general oncology and elaborated their own, a so-called “neurosurgical oncology” that focused on the development of neuronavigation and stereotaxic diagnostics and treatment of the MBT [14, 28]. Obsession with computer innovations led to the development of many stereotaxic radiosurgical and X-ray complexes, but we forget that the surgery in oncology is the demonstration of weakness in the science and misunderstanding of the basics of the biology of the MBT development [29-32]. We do not want to reduce the importance of surgical methods in oncology, but insist that the role of the surgery must be limited to the maximal primary (and rarely repeated) excision of the tumor mass in the brain, isolation of the biological material for diagnostics and production of individual preparation for the MBT therapy.

The standards recommended by the Association of Neurosurgeons in Russia [33] comply with the standards of the World Association of Neurosurgical Societies and are similar around the world, although they do not take into account the frontiers of genome and post-genome research of the MBT. The neurooncologist is trapped by the standards and options that were established in the beginning and end of the 20th century and is not able to think different.

The standards mostly concern about the neurosurgical care to the MBT patients. Contemporary “Standards and Options…” provide for a very convenient clinical position and legal form to excuse low effectiveness of the MBT therapy and high mortality rates.

Usually, at the first stage of the standard cancer therapy (surgery, chemo- and radiotherapy) and symptomatic administration of high doses of glucocorticoid hormones and antiedemics lead to the vigorous clinical restoration, stabilization of the patient’s condition, reduction of the neurological deficit, and a clear image that seems to confirm total elimination of the tumor in the brain. This phenomenon is easy to verify by MRI, PET and CT [34, 35]. The patient is discharged as the cured. However, it is well known that it is physically and technically impossible to eliminate the glial MBT in a surgical way. The phenomenon can be illustrated by the phase-contrast image of the experimental glial tumor (Figure **1**) that

demonstrates why surgery is unable to remove the whole tumor. The surgeon can remove only a visible part of the tumor. None of contemporary fluorescent dyes and nano-surgery [36] is able to visualize all existing focuses of perivascular growth of CCs. The effect of visual absence of the tumor in the brain and the consequent courses of chemo- and radiotherapy at the first stage of the therapy speak of allegedly real, although temporal, victory over the tumor. This therapy exhausts the patient's organism and conceals adaptation of the CCs to newly established aggressive environment.

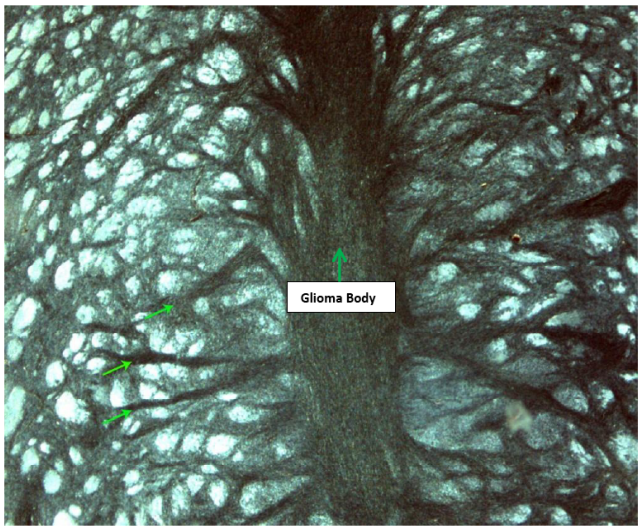


Figure 1: Phase-contrast imaging of glioma. Arrows point to the areas of perivascular invasion.

The first stage of "The standards and options…" almost completely depletes the resources of the available anti-cancer therapy of the MBT. The remission follows the first stage. The relapse is manifested in the repeated debut of neurologic deficit and continued tumor growth that in 95% of the cases are observed in 1-6 months in the bed of the removed tumor and two months post removal of the metastases in the brain [14]. Recurrent tumor requires repeated course of the complex anti-tumor therapy while the opportunity to provide real care to these patients is almost completely absent.

Therefore, the existing therapeutic universal standard, guidelines and options are ineffective and useless. Still, there is no choice and any alternative approaches are rejected by the global community of the oncologists and neurosurgeons. Another tragic feature of this standard should be noted: the concept of contemporary standard therapy does not imply the opportunity of high quality of life, even if the patient survives. In the case of MBT, the patient is destined to have dementia even if they are lucky to survive the therapy. Fifty gray of the recommended broad-field or local radiation of the brain for 3 to 5 years leads to chronic radiation sickness and rapid development of the brain cortex degeneration and, finally, to total dementia.

If we consider chemotherapeutic agents, massive chemotherapy with the inducers of apoptosis and other cytotoxic agents in therapeutic doses damages the brain, and it cannot be restored by available methods. The results of chemotherapeutic inducers of apoptosis are demonstrative (Figure **2**). Therefore, even theoretically, in the case of positive outcome, the patient with treated MBT faces the severe psycho-neurological disability with consequent progressing dementia and complete failure in social and family endeavor.

The available standard of the MBT therapy is the logical consequence of a ubiquitously acknowledged paradigm of contemporary anti-cancer treatment. It aims at complete elimination of all CCs in the body until complete cure. Ideologically and theoretically, this standard of anti-cancer treatment has only one goal, and, namely, total elimination of all CCs in the body in any possible way, and this is the fundamental methodological error.

Around the world, the neurooncology demands more and more new and potent chemotherapy drugs and novel equipment for radiation, and the industry meets these demands. It is noteworthy, that all of the innovations fit into the outdated paradigm of the MBT treatment aiming at the elimination of the CCs. To date, the cytoreductive approach to the MBT treatment [36, 37] was enriched by the technologies of the focused ultrasound ablation, photodynamic therapy, anti-cancer thermotherapy, stereotaxic radiosurgery using Gamma Knife or Cyber Knife systems, ultrafraction therapy and other [30, 31, 38]. The cytotoxic method is improved now by new target monoclonal technologies and personalized immune preparations [39], such as anti-cancer vaccines, activated cytotoxic leucocytes etc. [40-42]. The cytotoxic approach provided a methodological basis to the development of new nano-drugs [15, 37, 43, 44] and boron neutron capture therapy or proton radiation. The paradox of quality versus price does not bother anyone, as all medical industry and the Big Pharma live on it.

Probably, if in the previous two hundred years the oncologists and neurosurgeons did not succeed in the

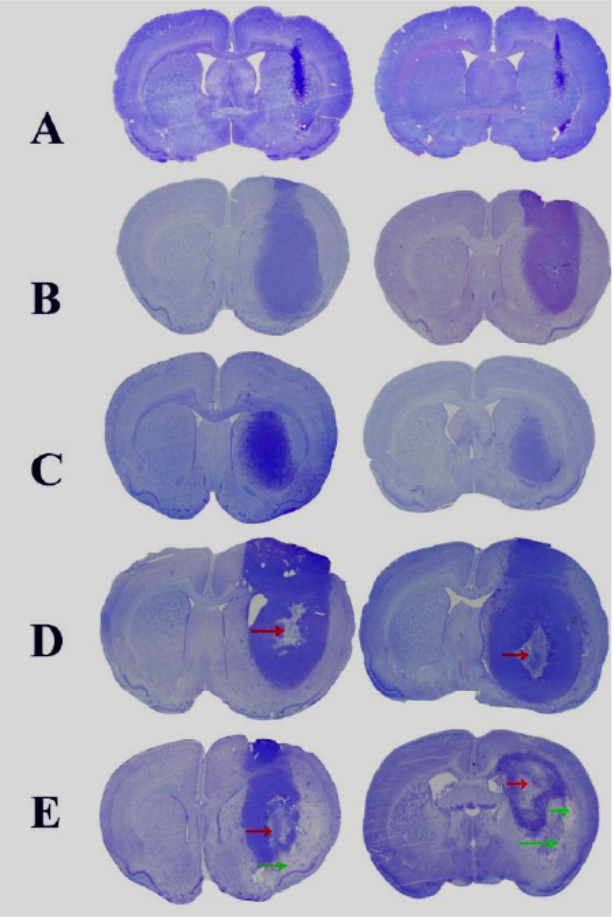


Figure 2: Morphometric analysis of glioma C6 volume after different treatments
A. Seven days old C6 glioma. (HSC and NSC transplantation). **B**. Control experimental glioma (no treatment). The volume of glioma is 220.3 ml. **C**. Experimental glioma after NSC (left) and HSC (right) implantation. Volume is 170.4ml; $p < 0.05$. **D**. Glioma after implantation of the transcriptome modified NSC (right) and HSC (left). Glioma volume is 360 ml. **E**. Intracerebral injection of ricin into tumor and peritumor area.
Red arrows point to foci of dying glioma cells. Green arrows show the foci of dying normal nervous tissue cells.

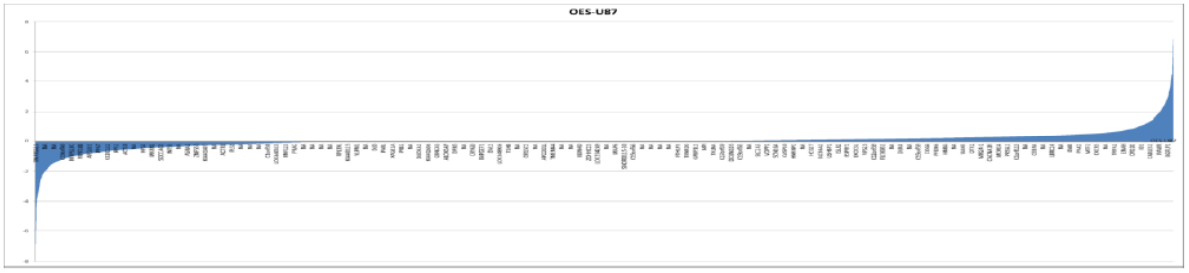
elimination of all cancer cells in the body of a patient, we should stop repeating our mistakes. Perhaps, we should eliminate only that part of the CCs that leads to severe cancer intoxication of the body, exhausts its adaptive resources and disorders the function of the organ, and other part can be “negotiated” and taken under control.

We presume that the problem of the survival of the CCs and CSCs is much deeper. Low effectiveness of various chemotherapy drugs and technologies in the elimination of the CCs is conditioned by the evolution of the somatic cells and their unique ability to develop the forms of life that are similar to the spores of the plants that are able to survive the unfavorable conditions of the environment and microenvironment.

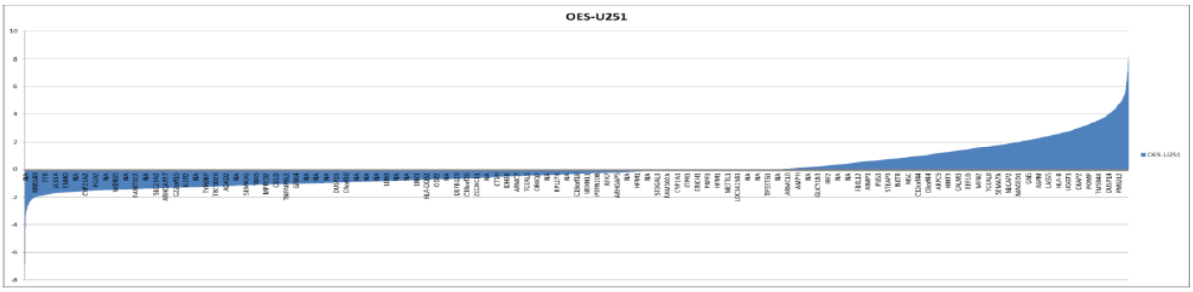
There is other biological reason for the impossibility to totally eliminate the CCs in the body. Almost all leading experts in oncology came to the conclusion that cancer and other malignant tumors are a genetic disorder of the nucleus of a tissue specific stem cell (TSSC) [45]. As a result of the mutational effect of various factors of carcinogenesis on the tissue-specific CCs, the CSCs with specific tumor phenotype develop, and they are the progenitors of all CCs clones of this tumor [46, 47]. There exist two complementary hypotheses of the origin of the CSCs of MBT. One supposes that they derive from mature gliocytes or other somatic cells by the activation of key genes of epithelial-mesenchymal transition (Snail, Twist, Slug, ZEB1, ZEB2, Lef-1) [48]. The second considers the development of the CSCs from the neural stem and progenitor cells of subventricular zones of lateral ventricles, granular layer of dental gyrus or other germinative zones of a mature brain of a human [24, 49]. Uniformity of key genes and epigenetic mechanisms that regulate life processes, commonality of immunocytochemical markers of cell surface (CD133+), identity of 63.5% proteins of proteomic profile [50] speak in favor of the hypothesis, according to which the CSCs of GBM come from neural SCs of the brain. Both types of SCs are capable for constant self-renewal, migration, high replication activity and multipotency [46, 51, 52].

Obviously, no matter how the CSCs were formed, it is impossible to eliminate them as any other somatic cell. The CSCs, as healthy SCs, will adapt and evolve in the unfavorable conditions of the microenvironment.

Our research [8, 53] of comparative proteome mapping and profiling of the normalized signal intensity of the CSCs in GBM of different lines (U251 and U87) and healthy NSCs showed that only 36.7% of total 1162 proteins are species-specific in the CSCs, while other oncospecific proteins are characteristic to Homo Sapiens. Same was observed in comparative whole transcriptome analysis of the expression of 29000 genes of neural SCs and CSCs (CD133+), isolated from GBM cell culture of U251 and U87 lines (Figure **3**). Hence, common regulatory signals of the microenvironment provide almost no effect on the CCs and CSCs, just as chemo- and radiotherapies. Meanwhile, the CCs lead to the irreversible mutations of normal regional SCs and healthy differentiated cells of the cancer patient. Therefore, an old methodological



Cancer SC MGB U87



Cancer SC MGB U251

Figure 3: The scheme of overlapped genes in the charts of expression of 29 000 genes of a neural stem cell (NSC), stem cell of U87 glioblastoma line and U257 glioblastoma line and their complete transcriptome profiles of gene expression.

approach that aims at the elimination of the CSCs is destined to fail. We should not go against nature and must not eliminate the CCs, but adapt to them and negotiate with the CSCs about their number and activity. Total elimination of the CCs and CSCs (by the methods of surgery, chemo and radiotherapy) will not arrest the unstoppable growth of malignant tumor, because the CCs and CSCs will evolve and adapt to new conditions.

According to Prof. Alexander Archakov [7], a healthy person has up to 500 thousand ($5x10^5$) CCs that circulate in a body, in pre-cancer the number of the CCs is up to 1 billion ($<10^9$), while in cancer the number of the cells is over 1 billion ($>10^9$). Therefore, even a healthy person has some number of the CSCs by default, but they are rigidly controlled by natural anti-cancer systems of a human body (regulatory cells of immune system and TSSCs). To an extent, at this angle the problem of cancer can be represented as the problem of the loss of control over reproductive effector functions of the physiological population of the CSCs and the uncontrollable growth of them and CCs, their progeny, capable of unlimited proliferation. The CCs and CSCs become uncontrollable only to usual growth-regulating mechanisms, but remain sensitive to extra-strong regulatory effects [54] or targeted effects [55, 56].

Viewed at this angle, the problem of cancer therapy can be presented as the problem of regulation and management of the number of the CCs and CSCs. The patient would be able to live with certain amount of the CSCs and CCs (up to 1 or 1.5 trillion), if their specific functioning, proliferative potential, and reproductive effector functions of the CSCs will be regulated and controlled by contemporary regulatory therapeutic means.

If we learn how to control the proliferative potential and number of the CCs and CSCs in the body, we would be able to transfer the disease from acute and fatal into chronic and non-lethal and considerably increase the survival rates. It can hardly be achieved by conventional pharmacological and therapeutic methods, as these cells are genetically modified, mutated somatic cells, and they are almost irresponsive to the standard signals of intercellular interaction. It is known that the CSCs respond to extra-strong signaling intracellular effects [9] and targeted effect, and, consequently, there is the chance to regulate them with intact and well manageable cell systems of the SCs and progenitor cells with specific properties [57]. A new paradigm of cancer therapy can be the following: control of the admissible number of the CCs and CSCs in the body, their regulation and compensation of the functional state in order to transfer

an acute fatal malignant process into chronic and non-lethal, to increase the survival rates and improve life quality of the patients.

We should refuse from the ideas of complete cure from cancer and malignant neoplasms, and solve the problem of regulation of the number of SCs and CSCs step by step. Hence, a basically new alternative stepwise paradigm of cancer and malignant tumors therapy is proposed. This methodological approach was termed the cytoregulatory therapy (CRT) in the complex therapy of the tumors [56] that should take its place along with cytostatic, cytotoxic and cytoreductive approaches (Figure **4**). The approach was described in details in several monographs and manuscripts in Russian, patented in the Russian Federation and summed up in the chapter *Proteome-Based Anti-Tumor Cell Therapy* of the *Topics in Anti-Cancer Research, Vol. 3* [50]. The concept of cancer and MBT treatment was presented in our article published in the Russian journal *Kletochnaya Transplantatsiya i Tkanevaya Ingeneriya* (*Cell Transplantation and Tissue Engineering*) [56] in 2010. The main idea of it is that we have to refuse from total elimination of the CCs and learn to control their number and their growth using autologous stem and progenitor cells with remodeled transcriptome profile.

The proposed method is highly technological, science-driven, individually tailored, targeted, low invasive, safe, showing low adverse effects and easy in its clinical application.

From the above said, we know that the clinical diagnostics of cancer is only possible when the number of the CCs exceeds 1 billion, *i.e.* the number of CCs > 10^9 [7].

All contemporary methods of treatment have their natural limitations as they have natural limits for elimination of certain number of the CCs (Figure **5**).

The relapse of cancer or malignant neoplasm testifies of the ineffectiveness of anti-cancer properties in the autologous immune competent cells (ICCs) of the patient and ineffectiveness of antic-cancer features of the HSCs and TSSCs. Hence, the restoration of natural anti-cancer properties of the ICCs, HSCs and TSSCs can be the main tool of a new paradigm of the tumor therapy that obligatorily includes the immune therapy and cytoregulation along with conventional methods.

At the first stage of the research (2005-2010) in animal models of the tumors, we used the technology of chemical induction of cell proteome by the inductors of apoptosis (viscumin, ricin) to remodel the proteome of the HSCs and TSSCs and showed technical opportunity to use the CRT for malignant tumors [8, 54]]. However, in practical experimental application of the CRT to the models of different tumors it became

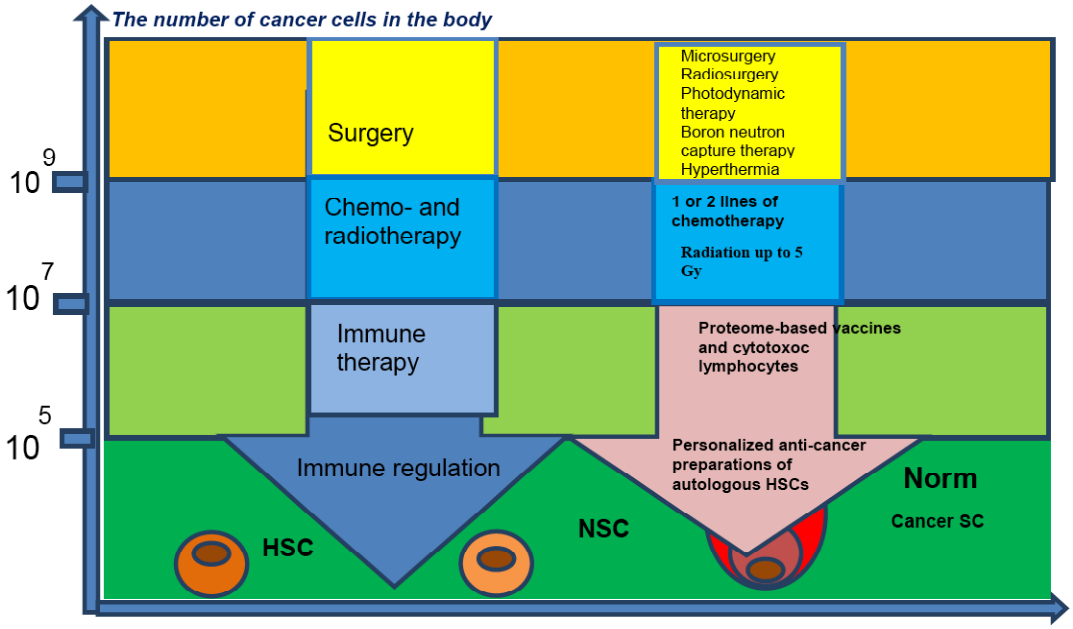


Figure 4: The role and place of post-genome (proteome and transcriptome) technologies in the complex therapy of malignant tumors of the brain.

Agent	Tumor	Point of Application	Mechanism	Effect	Authors
Tykerb	Breast cancer	Protein produced by HER2/neu gene	Eliminates HER2/neu of CSC	CSC percentage in tumour < from 11% to 5% in 63% -recovery.	Jenny Chang Baylor University December 2007
Gleevec	Chronic myeloleucosis. Medulloblastoma	BCR-ABL Signaling pathways	Inhibits BCR-ABL CSC signaling pathways	Blocks drugs targeting in CSC	National Cancer Institute (USA) 2001
Feverfew extract	Acute myeloleucosis	CSC of acute myeloleucosis	Parthenolide content blocks key enzyme of CSC proliferation	Induces suicide in acute myeloleucosis CSC not involving normal SC	Craig T.Jordan Monica Guzman, Rochester University
Rapamycin	Leucosis	Pten gene	CSC genes	Suppresses CSC growth and stimulates normal SC growth	Sean Morrison Michigan University 2007
Cyclopamine from Veratrum californicum extract	Prostate cancer Colon cancer Glioblastoma	Wnt and Sonic hedgehog signaling pathways	Inhibits Wnt and Sonic hedgehog signaling pathways	Suppresses CSC proliferation	Michael Din,2007 National Cancer Institute
Monoclonal antibodies to CD44 protein	Myeloid leukemia	CD44 Membrane marker of CSC	Blocks CD44 protein on CSC surface	Immobilizes CSC blocking migration pathways of CSC to the niches.	Princess Margaret Hospital in Toronto (Canada), 2007
Monoclonal antibodies to CD133+ protein	Colon cancer	CSC membrane marker	CD133+ Cells grow as tumor spheres	Block stem factor of CSC	John Dick et.al 2006 (Canada) Ruggero De Maria *et al.,* 2006 (Italy)
Adenoviral vector carrying interferon b gene	Glioma	Production of interferon b	Locally create high level of interferon –b in glioma	Antiproliferative and proapoptotic influence towards CSC	Nacamizo A.*et al*., 2005

Figure 5: Anticancer therapies targeted at the cancer stem cells.

obvious that the regulation of the CSCs and CCs must be extremely accurate and precise, and that the individual features, genomics, proteomics of the CCs and CSCs of specific tumors and SCs of the patient's organism must be taken into account (Figure **2**).

Further, we mapped, catalogued and profiled the proteins of the CSC and HSCs, NSCs and MSSCs isolated from the patients with GBM, lung cancer and breast cancer, and established a small number of proteins that can become crucial in the regulation and management of the growth of the CCs, which, if affected by healthy SCs and PCs of the patient with individually remodeled transcriptome, can control their number and their reproductive functions (expansion, angiogenesis, proliferation, migration and other) [8, 53].

Relying on contemporary concept of carcinogenesis of Peter Duisberg, who considers the carcinogenesis to be the form of speciation, we established that use of post-genome technologies in the analysis of the CCs and CSCs allows for finding an "Achilles heel" in their proteome, which is represented as the protein similarity matrix (SM) [8]. We detected a stable group of proteome targets for specific regulation of the CCs and CSCs by healthy SCs that have the same tissue-specific proteins. For it, the PP of the healthy SCs can be remodeled by chemical induction, purposefully modifying their transcriptome with low-molecular substances, or affecting the key proteins by appropriate microRNA to activate or suppress the key proteins genes expression. We proposed several methods of individual remodeling of the CCs proteome (avoiding

gene engineering) with consequent computer design of regulatory PP and biochemical remodeling *in vivo* and *in vitro*. The main stages of the technology are patented in the Russian Federation, the international PCT application are filed; they were presented at the international congresses and published in the journals [53, 56, 57].

This new post-genome and transcriptome evidence has the potential to lead to the modification of the available "Standard and options…" with regards to new knowledge. At the first stage, the standard treatment of the MBT must include the following: 1. The optimal microneurosurgery of the tumor; 2. Pharmaceutical chemotherapy drugs of the different lines of chemotherapy that were selected in the sensitivity tests of the culture lines of the patient's tumor cells; 3. Minimal cytostatic doses of ionizing radiation that were individually selected in cell cultures (the course dose is not more than 3 Gy); 4. After conventional treatments, every cancer patient should receive an obligatory course of immune therapy with well-known anti-cancer vaccines [41] and the preparations of CTLs; 5. The intrathecal transfusion of haploidentical HSCs of close relatives [58]. In the case of relapse, the consequent stages of the treatment should include all cytoreductive, cytostatic and cytotoxic approaches and end in the cytoregulatory personalized preparation with remodeled proteome [50].

Hereby, we propose our version of a new treatment standard and set of the options for effective therapy of the MBT and metastases to the brain:

The First Stage

1. Optimal microsurgical removal of the brain tumour. 2. Morphological analysis of the tumour tissue. 3. Culturing, standardization and cryopreservation of patient's CC line (PCCL). 4. Isolation and separation of the SCs. 5. Production of individual anti-tumour vaccines. 6. Individual selection of chemotherapy drugs according to the sensitivity tests of the PCCL. 7. The test for radiosensitivity of the CCs culture and detection of the minimal dose of radiation. 8. Production of the individual preparation of the autologous cytotoxic lymphocytes. 9. Mobilization and harvest of the stem cells of the first degree relative. 9. Endoscopic isolation of the sample of the olfactory sheath and culturing of the neural SCs for GBM, or biopsy of the bone marrow and culturing of the MSCSs for the cancer metastases to the brain. 10. Comparative proteome mapping and profiling of the CSCs and NSCs or MSSCs. 11. Whole transcriptome profiling of the CSCs and NSCs or MSSCs genes. 12. Production of the personalized anti-tumour cell preparation with specific regulatory anti-reproductive features. 13. First line chemotherapy according to the sensitivity test. 14. First radiotherapy (5 Gy maximal total dose). 15. Immune therapy with dendritic vaccines. 16. Intrathecal transplantations of hematopoietic SCs.

If no relapse, the oncological process is monitored every 3 to 6 months and the vaccine, immune modulators and intrathecal transfusions of HSCs are administered. The dose of the glucocorticoid hormones must be reduced to minimal.

If the tumour relapses, the second stage of the therapy is started: 1. The tumour is removed, the pathomorphological test is repeated and the CCs of the MTB are cultured. 2. The second line of chemotherapy is chosen depending on the sensitivity test and administered. 3. The dose of radiotherapy is chosen depending on the sensitivity test and administered (2 or 3 séances with the total dose not more than 5 or 6 Gy). 4. The cytotoxic lymphocytes are administered. 5. The autologous HSCs are harvested and cryopreserved. 6. The proteomic and whole transcriptomic mapping of HSCs, NSCs and CSCs genes. 7. The comparative bioinformation analysis to rpoduce the personalized anti-cancer preparation of the HSCs. 8. Administration of the personalized anti-cancer cell preparation.

If the tumour relapses, the third stage of therapy is started: 1. The stereotaxic radiosurgery (total radiation not more than 5 Gy) and radiotherapy of the tumour bed and neighbouring area. 2. The third line of chemotherapy that was previously chosen in the tests. 3. Administration of the CTLs. 4. Intrathecal administration of the personalized anti-cancer cell preparation.

If the tumour relapses, the fourth stage of the therapy is started: 1. The stereotaxic focused ultrasound ablation. 2. Radiotherapy of the tumour bed and neighbouring area (2 or 3 séances with the total dose not more than 5 Gy). 3. The third and fourth lines of chemotherapy that were previously chosen in the tests. 4 Administration of the CTLs. 5. Intrathecal administration of the personalized anti-cancer cell preparation.

The number of the therapeutic courses is not limited and depends on the number of relapses; the scope of chemotherapy must be minimal, not more than 2 lines at one stage; maximal dose of radiation must not exceed 5Gy at one stage.

CONCLUSION

The proposed standard of the MBT therapy that involves the post-genome technologies implements a basically new methodological approach to the therapy of the tumors, which is underpinned by novel paradigm of cancer regulation based on the regulation of the number of the CCs, control and management of the tumor growth, administration of accurately measured toxic chemotherapy agents and radiation, personalization of the anti-tumor treatment.

The approach can change the existing conventional ideology of the therapy of malignant tumors and transfer the methodology of complete elimination of cancer cells to the scientifically-driven platform of the production of anti-cancer cell agent that uses the advances of genome and post-genome technologies for the cytoregulatory therapy. The methodology of the cytoregulatory therapy in the standard of the MBT treatment, allows for the development of strict indications for all ionizing radiations, thus, considerably reducing such side effects as radiation necrosis and consequences of radiation disease. The uncontrolled and mortal neoplastic process will be turned into chronic and non-lethal disease that does not influence the life quality of the patient and only requires dynamic monitoring and repeated courses of already developed personalized cell therapy.

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CONFLICT OF INTEREST

No conflicts of interest.

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