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DENDRITIC CELLS IN GLIOBLASTOMA TREATMENT: A MODERN VIEW OF THE PROBLEM AND OWN EXPERIENCE

Glioblastoma (GBM) is the most aggressive primary malignant brain tumor in adults. The improvement of the efficacy of GBM treatment is an urgent problem encouraging the development of novel therapeutic strategies, in particular, immunotherapeutic modalities. With more understanding of the intimate interrelationships between the immune system and the mechanisms involved in cancer origin and progression, the skepticism related to the relevance of the immunotherapeutic approaches in the treatment of brain tumors is gradually decreasing. The review discloses the modern concepts on the association between CNS and the immune system. For a long time, CNS was considered as the immunoprivileged site that prevents the effects of immunotherapy in the treatment of brain tumors. Nowadays, these views are reconsidered, which opens the way to the use of immunotherapeutic approaches in GBM treatment. The results of the recent clinical trials on immunotherapy as a supplement to the conventional GBM treatment are considered. Vaccines based on the dendritic cell (DC) technology are regarded as the most promising for this purpose. The preliminary results of the Ukrainian clinical study are also presented and discussed. The results of the international clinical trials as well as our own experience give evidence of the relevance for using DC vaccines in the complex treatment of GBM, which is supported by the increased survival of patients and the safety of vaccine application. It is of high importance that GBM patients with the most unfavorable prognosis can benefit from DC vaccines as a component of the complex treatment. The prospects for immunotherapy in neurooncology are discussed.

Keywords: glioblastoma, immunotherapy, dendritic cell vaccination, survival.

Glioblastoma (GBM) is the most aggressive and the most common primary malignant brain tumor in adults [1]. It is extremely resistant to	therapy resulting in a rapid tumor recurrence and unfavorable prognosis with a median of the overall survival (OS) of 16—18 months even
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when the standard complex therapy is used including postoperative radiotherapy (RT) and chemotherapy (CTX) [2–4]. Furthermore, over the past four decades, the advancement in GBM prevention, early diagnosis, and treatment was the least among all other malignant brain tumors. While 5-year survival of patients with all brain malignancies increased from 23% in 1975–1977 to 36% in 2009–2015, for GBM these figures were 4% and 7%, respectively, in spite of the improvements in the surgery and the use of the alkylating CTX [5]. One of the features of GBM is its significant histological heterogeneity seemingly due to the difference in the mechanisms of tumorigenesis. GBM is characterized by selective permeability of blood — brain barrier (BBB), impairment of the functioning of the metabolic signaling transduction pathways, resistance to the therapy, immunosuppressive microenvironment, hypoxia, vasculogenesis, and neoangiogenesis. The highly organized interaction of these factors translates into high protumoral competence of GBM microenvironment [6].

Since the treatment outcome in GBM patients remains unsatisfactory, high hopes are put on the improvement of the treatment strategy including the involvement of immunotherapy. Over the years, the approach aimed at the activation of the immune system for the improvement of the treatment outcome in cancer patients has been a subject of scientific exploration. Recently, immunotherapy in cancer treatment including neurooncology is on a rise. There is a growing understanding of the combinatorial approach to the optimization of the treatment protocols for attaining the maximal synergy between immunotherapy and other treatment modalities [7].

At the same time, the skepticism about the clinical benefits of immunotherapy in the treatment of CNS tumors is nearly the biggest among oncologists. Nevertheless, the recently published data of the phase III multicenter clinical trial covering 94 sites in 4 countries from Au-

gust 2007 to November 2015 have demonstrated that the addition of vaccination with autologous tumor lysate-loaded dendritic cells (DC) to the standard care regimen extends the OS of patients with both newly diagnosed and recurrent GBM [8]. These results meet the expectations for a long-desired progress in GBM treatment and encourage broader involvement of immunotherapeutic methods in multimodal treatment of neurooncological patients.

This review has disclosed the recent literature data on the use of the immunotherapeutic strategy in GBM treatment along with our own data on the use of dendritic cell vaccine as a component of the complex treatment of newly diagnosed GBM.

Modern concepts on association between CNS and immune system

With more understanding of the intimate relationship between the immune system and the mechanisms involved in cancer origin and progression, the skepticism related to the relevance of immunotherapeutic approaches in the treatment of brain tumors is gradually decreasing. Nevertheless, some prejudice against the efficacy of immunotherapy in CNS malignancies still exists. One of the powerful arguments is the statement about the "immune privilege" of brain and spinal cord cancers preventing the response to immunotherapy. For a long time, CNS was considered a closed system beyond the reach of immunotherapeutic agents that is strictly safeguarded by BBB being devoid of any immune surveillance. Respectively, CNS cancers (especially GBM) were historically considered immunologically "cold tumors" unable to evoke a strong T-cell response. It was believed that this is the reason for the failure of previous clinical trials using immune checkpoint inhibitors for treatment of CNS cancers [9–11]. It is worth noting that earlier such malignancies as breast cancer, ovary cancer, prostate cancer, and pan-

creatic cancer were also regarded as "cold tumors" unable to respond to immunotherapy. Nevertheless, the current studies strictly demonstrate the response of such cancers to immune-mediated therapies [12].

In the historical aspects, the concept of "immune privilege" was questioned by the studies of Peter Medawar who as early as in 1948 demonstrated the rejection of the grafts in the brain [13]. Several subsequent studies substantiated this discovery. In particular, H-2 incompatible neural tissue transplanted to the brain of mice was recognized and rejected following the skin allografts for stimulation of the immune system [14, 15]. These data suggest that the allograft-specific adaptive immune response initiated on the periphery of the body could have an access to CNS and mediate the allograft rejection [16].

Technological progress allowing a direct visualization of immune cells in vivo using a multiphoton microscopy seems to cancel the concept of the immune privilege of CNS because of the discovery of the glymphatic system and meningeal lymphatic routes [17–19]. The glymphatic system is a unique system of perivascular channels formed by astroglial cells, which facilitate the efficient elimination of soluble proteins and metabolites from CNS by perivenous drainage pathways as well as the delivery of nutrients and active substances to brain parenchyma by the cerebrospinal fluid (CSF) influx along the periarterial space. In fact, the glymphatic system is the unique lymphatic system of the brain that functions similarly to the peripheral lymphatic system of the body [20].

As known, the immune surveillance, in particular the priming and activation of T-cells, occurs at the level of the meninges of the brain and spinal cord [21–23]. Nevertheless, only recently it has become clear how CNS is connected with the peripheral immune system. In 2015, two pivotal studies demonstrated for the first time a network of functional lymphatic vessels lining the dural sinuses and running into the deep cer-

vical lymph nodes. Such a system serves as a gate for T-cells transport connecting the periphery and the CNS liquor [19, 24].

Kipnis [25] demonstrated that antigens are drained from the brain parenchyma into the cerebrospinal liquor via lymphatic routes. Immune cells including T-cells may contact the cerebrospinal liquor in the functional meningeal lymphatic vessels [26]. Therefore, these meningeal lymphatic vessels may be a site of antigen presentation for cerebrospinal fluid-derived antigens [27]. In addition, immune cells may extravasate through the meningeal vessels and infiltrate the brain parenchyma in setting of the pathological conditions providing the entry of immune cells into the CNS. The meningeal adaptive immunity has been proved to play an important role mediating T-cell response to GBM. Furthermore, the liquor drainage from the meningeal lymphatic paths to the cervical lymph nodes is of importance for transporting DCs and antigens from the intracranial tumor to the periphery [28].

It became evident that the cells of the immune system have an access to three different CNS anatomical compartments, namely the cerebrospinal liquor, meninges, and parenchyma of the brain. Therefore, the continuous immune surveillance in CNS and its connection with the peripheral immune system are maintained, which is a prerequisite to the use of immunotherapy as a treatment modality for cancer of the brain and spinal cord [9]. Nevertheless, despite such potential, the requirement for overcoming BBB is still a major challenge on the way to the improvement of the efficacy of GBM treatment. This highly regulated barrier facilitates the transport of ions, neuromediators, and nutrients preventing at the same time the entry of neurotoxins and most macromolecules [29]. Small (< 400 Da) and lipid-soluble (< 8 H-bonds) molecules can passively diffuse through BBB [30], while the tight junctions represent a barrier limiting the transfer of large or water-soluble molecules [29]. This challenges the systemic immunothe-

rapy, relying on the effective delivery of antibodies to the tumor or the peripheral cell transfer. It is interesting that the loss of the BBB integrity and increase in its permeability are characteristic features of brain tumors [31]. This impairment of the BBB tightness is more significant in GBM due to the alterations of the major structural protein controlling BBB permeability, namely the loss of claudin-3 and the changed levels of claudin-1 and -5 expression [32, 33]. Although the BBB impairment could have been advantageous for drug delivery, especially those depending on recruiting the peripheral immune cells, the loss of the BBB integrity may also enhance the infiltration of pro-cancerous cells such as peripheral immunosuppressive macrophages [34]. It should be taken into account that in GBM, the BBB impairment is not total and some regions of intact BBB remain [35]. Therefore, the effectiveness of the systemic therapy of GBM cannot be provided without overcoming these limitations [34].

DC vaccines as a modern strategy of immunotherapy

Immunotherapy in general can be classified as active and passive. In passive (adoptive) immunotherapy, the ready-for-use immune effector molecules (monoclonal antibodies, modulators of the immune checkpoints, etc.) or immune cells are given to patients and are not produced within the patient's body. Active immunotherapy envisages eliciting the immunological response by the immune system. Both approaches can be specific or nonspecific. Specific active immunotherapy comprises different types of cancer vaccines based on the whole cancer cells, tumor DNA or RNA, DC, etc. Specific passive immunotherapy includes the use of monoclonal antibodies, cytotoxic T-cells, and tumor-infiltrating lymphocytes. The nonspecific active approach uses vector vaccines, BCG, heat shock proteins, cytokines, lymphokines, and immuno-

tropic agents of various origins. The nonspecific passive immunotherapy includes activated lymphocytes and macrophages. A separate group of adoptive immunotherapy is represented by live immunocompetent cells or their fractions capable of eliciting the cell-mediated immune response to tumor-associated antigens [36, 37]. This kind of active specific immunotherapy will be considered in more detail.

A plethora of the experimental studies confirmed that the immune system is capable to recognize and kill cancer cells [36]. The immunological response to cancer cells may be mediated by both cellular and humoral components of the immune system [38]. T cells of cancer patients demonstrate the reactivity directed toward the molecules of cancer cells obtained from tumor tissue including proteins and peptides originated due to the germline mutations in the genes associated with cell growth and differentiation [39, 40].

One of the most important discoveries in the field of cancer immunotherapy in the last decade is the evidence of the major role of specialized antigen-presenting cells such as DCs in the cell-mediated immune response. This discovery served as a basis for the design of DC-based cancer vaccines [41]. Vaccine therapy with autological DCs is considered one of the most promising approaches in cancer immunotherapy. This approach has demonstrated its efficacy for the broad spectrum of cancers such as lung cancer, ovary cancer, gastric cancer, renal cancer, prostate cancer, and hematological malignancies [42–44]. In 2010, DC vaccine for treating hormone-refractory prostate cancer became the first DC vaccine approved by FDA [45]. This event reinforced the conviction in the relevance of supplementing the multimodal treatment of cancer patients with immunotherapeutic technologies.

Moreover, the functional capability of DC in CNS was confirmed contrary to the previous concepts denying the possibility of using DC vaccines in brain cancer. Earlier, only cells

of microglia were considered as such possessing antigen-presenting functions [46, 47]. In fact, today it is clear that cells of microglia possess significant plasticity and can be shaped as macrophage-like or DC-like cells depending on the activation stimulus [48, 49].

The large immune potential of microglia is one of the arguments for overcoming skepticism as to the relevance of active specific immunotherapy in neurooncology. Nevertheless, one cannot ignore the fact that immunotherapy of brain malignancies is much more complicated as compared to other solid tumors because of the infiltrative nature and complex architecture of GBM [36].

Due to their inherent properties, DCs serve as modifiers and stimulators of the antigen-specific antitumor immune response. The immature DCs in the peripheral tissues capture antigens and process them to peptide fragments, which initiate DCs maturation and migration to the lymphoid organs, where they complete the maturation process to present antigen and stimulate naïve T lymphocytes. The mature DCs represent tumor-associated antigens in complex with the molecules of histocompatibility MHC I and II to naïve T cells and primed T cells, which finally results in the activation of the cells related to the adaptive cell-mediated immunity — specific CD4⁺ helpers and CD8⁺ cytotoxic T cells as the major effectors of the antitumor immune response. The DCs maturation is correlated with up-regulation of the cytokine cascade (IL-12, IL-2, IFN- γ , etc.) and the second activation signal mediated by co-stimulatory molecules (CD86, CD80, CD58, CD54) expressed on the mature DCs. On the other hand, DCs are able to activate the cells of the innate immunity such as NK and NKT cells [50, 51].

Therefore, the major function of DCs consists in their involvement in generation and/or enhancement of the immune response by presentation of a large amount of captured and processed antigens in complex with MHC molecules and

various auxiliary molecules interacting with T cell receptors and inducing primary and secondary immune responses as well as the immunological memory [9].

The general methodology for preparing DC-based antitumor vaccines can be summarized as follows: DCs that are generated *ex vivo* by culturing hematopoietic progenitor cells or monocytes with cytokine combinations, are loaded with appropriate antigens. Upon inducing the maturation of the antigen-loaded DCs, they are administered to patient subcutaneously. An antitumor effect of the DC-based vaccines is attained by repeated vaccination in monotherapy regimen.

It should be noted that, contrary to CTX and other methods of cancer treatment aimed at the direct killing of cancer cells, DC-based therapy focuses on the enhancement of the specific anti-cancer immune response along with decreasing side effects [52]. Nevertheless, there are many pitfalls in DCs clinical application. The major obstacles for the use of DC-based vaccines are tumor-mediated immunosuppression and/or insufficient functional activity of *in vitro* generated DCs [53]. To eliminate these problems, the ongoing studies are aimed at the rational combination of different treatment strategies. For example, DC-based vaccines are combined with cyclooxygenase inhibitors or inhibitors of VEGF [54]. Low doses of gemcitabine and cyclophosphamide may be used for inhibiting myeloid-derived suppressor cells or Treg cells [55]. A promising approach consists in combining DCs with recombinant hematopoietic, pro-inflammatory or T cell cytokines (Flt-3L, GM-CSF, CD40L, IL-2, IL-12, IFN- α , IFN- γ) [56]. Recently, low-molecular tyrosine kinase inhibitors (sunitinib, vemurafenib), mTOR inhibitors, and others have also been used in combination with specific immunotherapy [57]. The search for the optimal solutions to enhance the efficacy of DC-based vaccines never ends. Combination of different modalities of immunotherapy with chemothe-

rapy and targeted therapy may be advantageous for increasing substantially the efficacy of the GBM treatment.

Clinical trials on immunotherapy in GMB patients

The number of publications summarizing the results of clinical trials of DC-based vaccines in GMB is not high. Searching for such publications in PubMed, we have found fewer than 50 papers related to the randomized and non-randomized clinical trials on this issue. Above half of them were published between 2011 and 2020.

It should be mentioned that the overall number of publications on the clinical trials of DC-based vaccines in different cancer types over the same period is much more abundant.

The efficacy, safety, and immunological response through adding DC vaccines to the multimodal treatment of malignant gliomas, both primary and recurrent, have been the priority focus of research. Most of the publications have reported a favorable survival for DC vaccine-treated cohort compared to the standard treatment. There have been no severe adverse events (grade III/IV) observed. A complex immunological responses following adjuvant DC vaccines were investigated with the attempts to identify subgroups of GBM patients more responsive to DC-based specific active immunotherapy. The relatively modest number of study cohorts and the initial phases of the respective clinical trials are by far the most significant limitations of these studies. However, it should be noted that all the researchers emphasized the promising prospects of this issue in neurooncology and the need for further studies. It is fair to add that the initiative in this area belongs to the researchers from the United States, People's Republic of China, Japan, and Western Europe [58–61].

Several publications deserve to be highlighted.

In 2022, the systematic review and meta-analysis published by Cozzi et al. [36] as an Italy —

Iran research cooperation presented the results of the database search related to the use of immunotherapy in the GBM treatment. Among the 157 screened, only 15 articles were eligible for the final analysis. The authors have shown that the use of DC vaccines can lead to the increased 1- and 2-year survival of GBM patients by 1.9 and 3.6 times, respectively. The conclusion made from this study is that antitumor regimens including DCs can effectively improve a mid-term survival in GBM patients, but their impact became evident only after one year following the vaccination. These data indicate the need for more time to achieve an anti-GBM immune response and suggest the use of additional therapeutics, such as checkpoint inhibitors, to empower an earlier DC vaccination effect in patients with poor prognosis.

In 2023, the long-desired progress in complex GBM treatment within the addition of the DC-based vaccine was finally clearly demonstrated. The report of the phase III multicenter prospective externally-controlled cohort trial covering 94 sites (ClinicalTrials.gov Identifier: NCT00045968) confirmed that the addition of the DC-based vaccine to the standard care allows for a significant improvement of the GBM treatment outcome [8]. A median OS for 232 patients with newly diagnosed GBM receiving DC-based vaccine was 19.3 (95% CI, 17.5–21.3) months from the beginning of immunotherapy (a median of 3.1 months after surgery) vs. 16.5 (95% CI, 16.0–17.5) months in the placebo group (HR = 0.80; 98% CI, 0.00–0.94; $p = 0.002$). The survival at 48 months was 15.7% vs. 9.9%, and at 60 months 13.0% vs. 5.7%.

For 64 patients with recurrent GBM who received DC-based vaccine, a median OS was 13.2 (95% CI, 9.7–16.8) months from relapse vs. 7.8 (95% CI, 7.2–8.2) months in control patients (HR, 0.58; 98% CI, 0.00–0.76; $p < 0.001$). Survival at 24 and 30 months after the recurrence was 20.7% vs. 9.6% and 11.1% vs. 5.1%, respectively.

Moreover, additional benefits of DC-based vaccines were demonstrated in patients with the methylated *MGMT* promoter. Median OS in this group (N = 90) was 30.2 (95% CI, 23.7–33.9) months from the beginning of immunotherapy compared to 21.3 (95% CI, 18.3–25.1) months for external control population (N = 199) (HR, 0.74; 95% CI, 0.55–1.00, $p = 0.03$).

An analysis of the progression-free survival (PFS) was hampered because of the generally accepted problems related to distinguishing true progression from pseudo-progression (including vaccine-induced immune cell infiltration). An analysis of more than 50% of the images, in which possible progression could be observable by radiologists, demonstrated discrepancies in the interpretation.

The DC-based vaccines were tolerable: of 2151 total vaccine doses administered, only 5 serious adverse events were recorded (3 cases of intracranial edema, 1 case of nausea, and 1 case of lymph node infection). No autoimmune reactions or cytokine storm among the patients who received DC-based vaccines were demonstrated.

Several important points are worth noting. Although the absolute survival was greater in patients with positive prognostic factors, the relative survival benefit was larger in certain categories of patients who usually demonstrate a worse course of the disease in setting of the standard care (older patients, patients with substantial residual tumor, and patients with recurrent disease). These results are encouraging, suggesting the prospects of using DC-based vaccines in a broad range of clinical settings in patients with brain tumors. In general, the results of this clinical trial have demonstrated significant progress in increasing survival of GBM patients when the standard therapy is supplemented with immunotherapy.

In 2023, the results of another clinical trial studying the effects of immunotherapy in GBM were published. In this trial, nivolumab (NIVO), a fully human monoclonal antibody to the pro-

grammed cell death 1 protein (PD-1) immune checkpoint was assessed as a supplement to a standard RT as compared to combination of RT with temozolomide (TMZ) [11]. The patients under study were with newly diagnosed GBM with an unmethylated *MGMT* promoter, i.e. the patients with predictably worse prognosis according to the molecular-biological features. 560 patients were randomized, 280 to each arm (RT 60 Gy + NIVO or RT + TMZ (75 mg/m² daily during RT and 150–200 mg/m²/day 5/28 days during maintenance). The complete surgical resection had been performed in 151 patients (53.9%) in the NIVO + RT arm and 144 patients (51.4%) in the TMZ + RT arm. The median OS was 13.4 months (95% CI, 12.6–14.3) in the NIVO + RT arm and 14.9 months (95% CI, 13.3–16.1) in the TMZ + RT arm (HR, 1.31; 95% CI, 1.09–1.58; $p = 0.0037$). Median PFS was 6.0 months (95% CI, 5.7–6.2) in NIVO + RT arm vs. 6.2 months (95% CI, 5.9–6.7) in TMZ + RT arm (HR, 1.38; 95% CI, 1.15–1.65).

Therefore, the results of this study do not indicate that NIVO can be a replacement for CTX with TMZ, and benefits of such a kind of immunotherapy, in contrast to DC-based vaccines in the previous study, have not been demonstrated.

Our own experience of using DC-based vaccination in GBM treatment

The prospective single-center non-randomized clinical study performed at the SI “Romodanov Institute of Neurosurgery, NAMS of Ukraine” (RIN) in 2018–2022 aimed at surveying the efficacy of the DC-based vaccine supplementing the complex GBM treatment. The study was approved by the Ethics Committee of the RIN. The preliminary results of this study are presented below.

The primary end-point of the study was the OS of patients with newly diagnosed GBM from the date of the surgery and the survival from the be-

ginning of DC-based vaccination. The secondary end-point comprised the analysis of the factors affecting the survival of the patients under study as well as the safety of DC-based vaccine used. The adverse events throughout the study were assessed according to the National Cancer Institute Common Terminology Criteria version 3.0. https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/ctcae_v3.pdf.

24 patients (14 males and 10 females) aged 31–70 with the pathomorphologically confirmed diagnosis of GBM grade 4 of anaplasia according to the WHO classification [62] without *IDH1 R132* mutation (IDH of wild type) were enrolled in the study. Half of the patients had a methylated promoter of the *MGMT* gene. In 16 patients, a radical surgical tumor resection ("total" or subtotal) was performed, and in 8 patients, a partial tumor resection was provided. Following the surgery, all patients received adjuvant chemoradiotherapy. Hypofractionated RT was performed at a total boost dose of 52.5 Gy in 15 fractions, 5 days a week on a linear accelerator Trilogy (USA) (6 MeV) using an intensity modulated technique.

The concomitant CTX TMZ was provided according to the standard outlined by The European Organization for the Research and Treatment of Cancer (EORTC) [63]. The chemoradiotherapy course was followed by the maintenance TMZ (150–200 mg/m²/d × 5 days, every 28 days, at least 6 cycles).

At the beginning of immunotherapy, the functional status of all patients scored ≥70 by the Karnofsky performance scale, ≤1 by ECOG scale.

For each DVC, DCs were generated from peripheral blood monocytes cultured with GM-CSF, IL-4, LPS, and IFN-α [64], loaded with lysate of tumor cells, and injected intradermally paravertebrally at the scapula site on Day 8 from initiating DC culture. To prepare the tumor lysate, a cell suspension was first obtained followed by filtration, concentration to 107 cells/ml, 5 freeze/

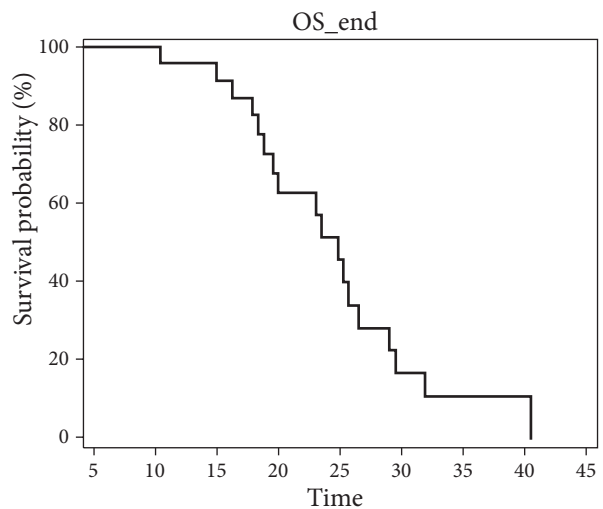


Fig. 1. Kaplan — Meier plot of OS (from the date of surgery) for 24 GBM patients treated with DC-based vaccine that supplemented the adjuvant complex treatment

thaw sequential cycles ($T = -20\text{ }^{\circ}\text{C}/+37\text{ }^{\circ}\text{C}$), and centrifugation. Subsequently, the tumor cell lysate was kept frozen in aliquots at $T = -20\text{ }^{\circ}\text{C}$ and was used during the DCV treatment course. For each vaccination, part of the tumor cell lysate was thawed. Standardization of the tumor cell lysate by the number of cells to be obtained, the amount of protein and RNA was mandatory. DC vaccine was administered once a month, one course comprises 6 injections, 3–5 courses in total with alternating adjuvant CTX courses.

By March 01, 2023 (the point of cessation of data collecting), 18 patients had died, 6 were still alive. The median follow-up was 31.3 (95% CI, 22.7–36.5) months. The median OS (from the date of surgery) was 24.8 (95% CI, 19.4–26.4) months with 18-month survival of 78% and 24-month survival of 52% (Fig. 1). The median OS from the beginning of immunotherapy was 19.7 (95% CI, 15.8–21.9) months.

The analysis demonstrated that the significantly higher OS was associated with the radical surgery ($p < 0.0001$), methylated *MGMT* promoter ($p < 0.0001$), and high functional status (80–90 points scored by the Karnofsky scale) at the beginning of immunotherapy ($p < 0.0001$).

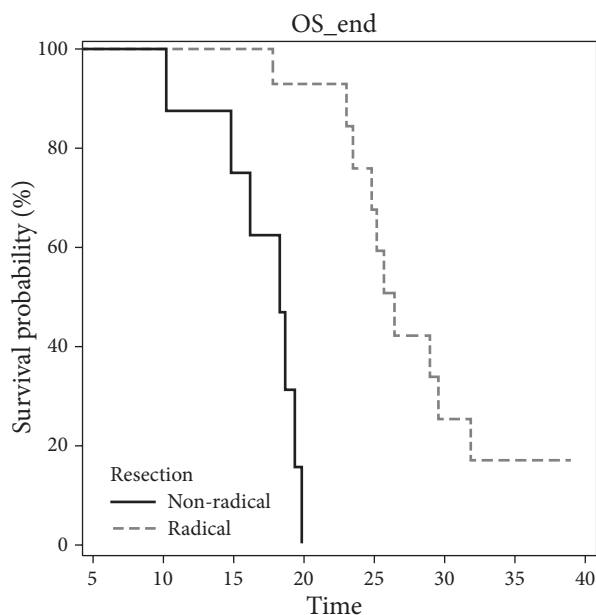


Fig. 2. Kaplan — Meier plot of OS (from the date of surgery) for 24 GBM patients treated with DC-based vaccine that supplemented the adjuvant complex treatment dependent on the extent of surgical resection

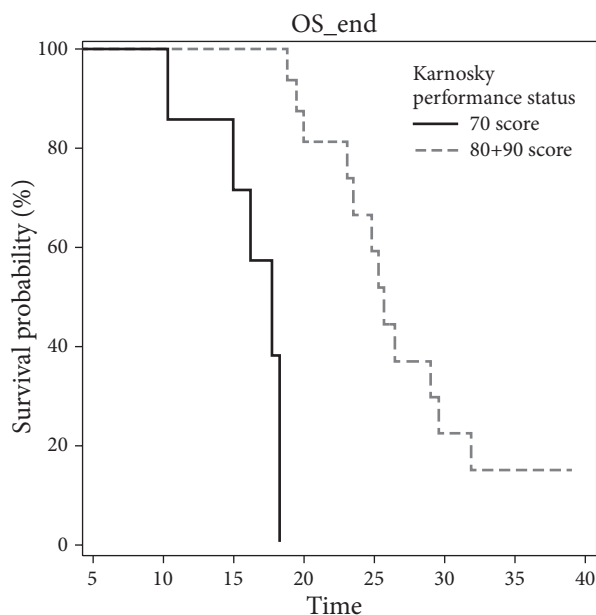


Fig. 4. Kaplan — Meier plot of OS (from the date of surgery) for 24 GBM patients treated with DC-based vaccine that supplemented the adjuvant complex treatment dependent on the functional status assessed by the Karnofsky scale

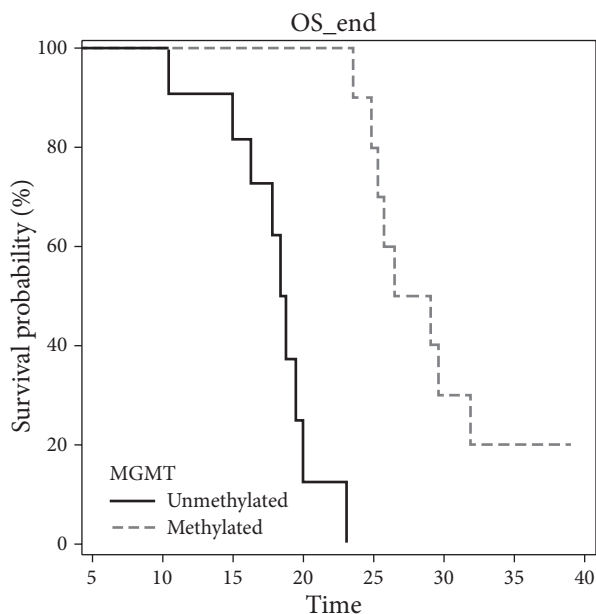


Fig. 3. Kaplan — Meier plot of OS (from the date of surgery) for 24 GBM patients treated with DC-based vaccine that supplemented the adjuvant complex treatment dependent on the methylation of *MGMT* promoter

At the same time, the age at diagnosis (≥ 60 vs. < 60) and gender did not affect OS ($p = 0.5583$ and $p = 0.4215$, respectively) (Figs. 2—4).

A death risk in the setting of DC vaccine was less in patients with radical tumor resection (log-rank $p < 0.0001$, HR = 0.17; 95% CI, 0.04—0.8) or in patients with a methylated *MGMT* promoter (logrank $p < 0.0001$, HR = 0.16; 95% CI, 0.06—0.6).

In no case, serious adverse events requiring hospital admission were observed. In 4 patients, the transitory hypothermic reaction was observed within 1—6 h following DCs injection.

Besides the clinical effects, DC-based vaccine resulted in decreasing the count of myeloid-derived suppressor cells and T-reg cells, which are known as cells suppressing immune surveillance and facilitating tumor development [64].

The detailed analysis of the results of this clinical trial will be presented in a separate paper.

Prospects for immunotherapy in neurooncology

Modern immunotherapy amalgamates the broad spectrum of the approaches with the administration of DC-based vaccines being one of the promising treatments taking into account the key regulatory role of DCs in the formation of immunological antitumor response as well as the potential precision of their effects.

An analysis of the current literature demonstrates that the skepticism related to the role of immunotherapy in neurooncology gives a way to modest optimism. Such breakthrough became possible thanks to the deepened understanding of the association between CNS and immune system, which abrogated the concept of the immune privilege of CNS. Meanwhile, progress has been attained in the development of immunotherapeutic technologies focusing on more precision of the effects of immunological treatment modalities. Finally, the clinical experience demonstrated survival benefits when the multimodal treatment of brain cancer is supplemented with immunotherapy.

Our own experience as well as the results of international clinical trials give evidence of the relevance for using DC-based vaccines in the complex treatment of GBM supported by the increased OS and safety of vaccine application. It is important to notice the benefits of such an approach in treatment of GBM patients with most unfavorable prognosis (cases of tumors with unmethylated *MGMT* promoter, aged patients, patients with low functional status, and cases of non-radical surgery). This aspect is of high importance since the low susceptibility to the standard therapy due to the biological features of tumor or patient-associated factors is believed to be the major reason for the unsatisfactory treatment outcomes in GBM patients.

The larger cohorts of patients, the longer follow-up, and the correct stratification of patients to decrease the effect of non-homogeneity of

the studied cohorts will allow the application of more potent methods of the statistical analysis for increasing the evidence level of the obtained results and delineating the categories of GBM patients who will benefit most from the use of DC-based vaccines. The prolongation of the follow-up will provide the opportunity for obtaining refined data on the patients who survive for at least 5 years from diagnosis. Of particular interest is the study of the action of DC-based vaccines in the complex treatment of recurrent GBM since such patients have the worst prognosis. Some data demonstrate that there are patients who survive long after the completion of immunotherapy with DCs, which may be associated with the effective immunological memory. It is worth noting the data by Liao et al. [8] demonstrating 13% level of 5-year survival of patients whose complex treatment was supplemented with DC-based vaccines, especially in cases with poor prognosis of the standard therapy. By the demonstrated long-expected progress, this study discussed above in detail, it may be well compared with the remarkable study by Stupp et al. [65].

It is interesting that as early as in 2000, Liao et al. [66] reported the first clinical case of the use of DCs in a patient with malignant recurrent glioma located in the brainstem who survived for 21 months from the date of diagnosis. It was during this period when the clinical trials in phase I on the immunotherapeutic treatment of malignant glioma started [8, 67, 68].

Currently, such factors as tumor-mediated immunosuppression and insufficient functional activity of *in vitro* generated DCs are considered the major obstacles to increasing DC vaccine efficacy [53]. Several reasons for the suboptimal clinical results of using DC-based vaccines comprise also aspects related to the sources of DC generation, DC migration to the lymph nodes, selection of antigens for activation of CD8⁺, CD4⁺ T-cells, low cytotoxicity of DCs, and immune dysfunction in the advanced stages of can-

cer. There are several mechanisms allowing cancer cells to elude immune surveillance. Among them are angiogenesis induction, involvement of immune cells-suppressors, upregulation of several inhibitory molecules in the immune system; a complex of these factors significantly affects the efficacy of anticancer responses [69].

Based on the above, a combined immunotherapy aiming to form a sustained and precise anticancer response is considered a topical strategy for improving the clinical results of DC immunotherapy [69–71].

Today it is clear that immunotherapy is capable of enhancing the endogenous antitumor immunity making it a promising approach in neurooncology. Nevertheless, many aspects of the practical implementation of immunotherapy are still pending, especially the optimal regimens and sequence of the administration of the agents. Equally important is the assessment of the prognostic factors related to better survival. The answers to these questions will allow attaining further progress in treating

GBM, which are the most aggressive tumors in clinical practice.

The benefits of the autologous DC-based vaccines for the survival of GBM patients have been convincingly demonstrated by the results of the phase 3 prospective randomized multicenter clinical trial as well as the preliminary results of the Ukrainian clinical trial analyzed in this review. DC-based vaccine as a supplement to the conventional GBM treatment allows increasing survival especially in patients with more unfavorable prognosis who are less susceptible to the standard treatment.

Therefore, the concept of the immune privileges of CNS has been canceled, and the potential response of malignant gliomas to the immune-mediated action has been proved.

The ongoing study aimed at improving immunotherapeutic approach as a component of multimodal treatment of GBM involving more numerous cohorts of patients with long-term follow-up is undoubtedly one of the priorities of the current scientific inquiry in neurooncology.

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ДЕНДРИТНІ КЛІТИНИ В ЛІКУВАННІ ХВОРИХ НА ГЛІОБЛАСТОМУ: СУЧАСНИЙ ПОГЛЯД НА ПРОБЛЕМУ І ВЛАСНИЙ ДОСВІД

Гліобластома (ГБМ) є найбільш агресивною з первинних злоякісних пухлин головного мозку в дорослих. Покращання ефективності лікування хворих на ГБМ є нагальною проблемою, що заохочує розвиток нових терапевтичних стратегій, зокрема, тих, що базуються на застосуванні імунотерапії. З поглибленням пізнання тісних взаємозв'язків між імунною системою і механізмами виникнення та прогресування раку, скепсис щодо доречності імунотерапевтичних підходів до лікування пухлин головного мозку поступово слабшає. В огляді розглянуто сучасні концепції щодо асоціації між ЦНС та імунною системою. Впродовж тривалого часу головний мозок вважався імунопривілейованим органом, що унеможливлювало імунотерапію пухлин ЦНС. Зараз ці погляди змінюються, що відкриває перспективи для застосування імунотерапевтичних підходів до лікування хворих на ГБМ. Наведено результати нещодавніх клінічних досліджень, де імунотерапія застосовувалась як додатковий метод до традиційної схеми лікування таких хворих. У цьому аспекті вакцини, що базуються на застосуванні дендритних клітин (ДК), розглядаються як найбільш надійні. Подано та обговорено також результати проведеного в Україні клінічного дослідження із застосування ДК у хворих на ГБМ. Результати міжнародних клінічних досліджень та наш власний досвід свідчать про доцільність застосування таких вакцин у комплексному лікуванні хворих на ГБМ. На користь цього свідчать дані щодо покращання показників виживаності та безпечності застосування цих вакцин. Дуже важливим є той факт, що такі вакцини допомагають і хворим на ГБМ з найбільш несприятливим прогнозом. Розглянуто перспективи імунотерапії в нейроонкології.

Ключові слова: гліобластома, імунотерапія, дендритно-клітинна вакцинація, виживаність.