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Introduction to dendritic cell vaccines immunotherapy for glioblastoma multiforme: A novel approach



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ABSTRACT

Background: The modality of therapy in this era is quite sophisticated. The mortality rate of patients diagnosed with glioblastoma multiforme is still high. It might be due to the late diagnosis of the tumors since most in the early stages some tumors do not show any significant symptoms or the symptoms usually misdiagnosed with another disease. Nowadays there is an uptrend of therapeutic methods called immunotherapy which declared as the fourth approach for glioblastoma multiforme (GBM). In RSPAD Gatot Soebroto Jakarta, the author starts this approach using dendritic cell vaccines in the specialized department called the Indonesia Army Cell Cure Center.

Aim: The report aims to describe a case of GBM treated by dendritic cell vaccines.

Case Report: A 52-year-old woman had weakness in her left extremities and visual impairment in the left eye since 2016. The patient was brought to RSPAD in August 2016 with a history of cerebral hemorrhage, then already underwent a craniotomy at the right temporoparietal region. After

biopsies and tissues examination, the patient later diagnosed with GBM. As for judging the natural history of the diseases, the team decided to counsel the patient and her family conducting a new treatment strategy for GBM, immunotherapy. The immunotherapy approach performed in RSPAD was the dendritic cell (DC) vaccines therapy. As regard to post-DC vaccines therapy, the patient showed a significant improvement in her clinical condition (Karnofsky performance status increased from 30% to 60%). Also, the patient surpassed the average survival rate. Thus, the patient still scheduled for a routine follow up and a round of examinations to preserve the patient improved condition.

Conclusion: The patient who has immunotherapy strategy especially dendritic cell vaccines therapy has shown an improved clinical status and survival rate for GBM, more than the average survival rates. These findings might give us more insights into how dendritic cell vaccines therapy can be involved as the fourth therapeutic strategies on treating patients with GBM.

Keywords: dendritic cell therapy, glioblastoma multiforme, immunotherapy

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INTRODUCTION

The case of glioblastoma multiforme (GBM) has been known to be the most malignant and often the most occurring type of primary astrocytomas. Reportedly it accounts for more than 60% of all brain tumors in adults population.¹ The first surgery on a patient with this type of tumor was performed in Vienna around 1904.² Even though GBM is quite a rare tumor case with a global incidence of fewer than 10/100,000 people, the poor prognosis with a survival rate of 14-15 months after diagnosis makes the situation is a crucial public health issue.^{3,4} The long-term survivors, defined as those who are alive 3 to 5 years following diagnosis, are rare and young age is their only common feature.⁵ In spite of its seemingly low incidence, the mortality rate of GBM cases accounts for 3%–4% of all cancer deaths each year in the United States.⁶ The Anatomy and Pathology Department in RSCM since 2001-2010 reported that the astrocytomas were around 179 case or about 20% of all intracranial tumor, 12 cases of anaplastic astrocytoma, and 42 of glioblastoma.⁷

The incidence rate of gliomas are higher in western than less developed countries due to the fewer awareness of reporting the gliomas, limited access to the medical centers, and differences in diagnostic practices.^{8,9}

GBM is the most aggressive, invasive, and undifferentiated type of tumor, and therefore has been designated as Grade IV by WHO.^{10,11} In 1940, the German neuropathologist Joachim Scherer presented his concept that glioblastomas (GBMs) could be divided into “primary” and “secondary” as well as these types are based on their histological and clinical features.¹² The majority of GBM cases are mostly primary, and these patients tend to be in older aged and have a poorer prognosis than patients with secondary GBM.¹²⁻¹⁶

GBM is rare in the cerebellum and spinal cord, and fewer than 10% of cases are found in children, in which the brainstem is affected more commonly than in adults.¹⁷ GBM occurs most frequently in the subcortical white matter of the cerebral hemisphere. In a series of 97 glioblastoma cases from University Hospital Zurich, the most frequently affected sites

were the temporal (30%), parietal (24%), frontal (23%), and occipital (16%) lobes.¹⁸

The presentation of a patient with newly diagnosed GBM can vary greatly depending on the size and location of the tumor and the anatomic structures of the involved brain.¹⁹⁻²³ As for the diagnosis of GBM, imaging techniques carried out include invasive procedures such as catheter angiography and non-invasive tests such as computed tomography (CT) and magnetic resonance imaging (MRI) scans.²⁴ MRI is believed to be the primary diagnostic tool for GBM. The tumor diameter at the time of diagnosis usually has a size of approximately 4 cm.²⁵ On the other hands, as for a definitive diagnosis, a histopathological test needed.²⁶ When neurosurgical tumor resection is not possible, fine needle aspiration biopsy is performed.²⁷⁻³⁰ The addition of radiotherapy to surgery has increased survival rate from 3-4 months to 7-12 months.^{18,31} Besides, the tolerance of healthy brain tissue due to radiation is limited as the increased risk of radiative necrosis.³²⁻³⁴ Blood-brain barrier limits the distribution of the chemotherapy drug that drives another approach.^{35,36}

Furthermore, the doctors want to minimize all the limitations of recent treatment strategies of GBM and increase patient survival rates. The immunotherapy for cancer has been verified improving clinical effect in various clinical trials.³⁷ Immunotherapy can mobilize the immune function to resist and ultimately eliminate the cancer cells. It enhances anti-tumor immunity by stimulating and mobilizing its immune system, and control as well as kill tumor cells by human intervention. Immunotherapy is a promising treatment option and is considered to be fourth cancer treatment.^{38,39}

Dendritic cell (DC) is the strongest professional antigen-presenting cells (APC). It can efficiently uptake, processing, and presenting antigens. Immature DC has strong ability of migration. The mature DC can effectively activate naive T cells as well as initiate, regulate, and maintain a central role in the immune response.⁴⁰⁻⁴⁵ DC as a prepared vaccine is used as immunotherapy for GBM patients which improves the short-term survival rate.⁴⁶ The mechanism of DC vaccines can be specified as two stages of induction of the immune response. The primer stage is in immune response and as immune stimulators. Activated DC interacted with cytotoxic CD8 T cells and expanding the tumor-specific CD8 T cells then finally the tumor-specific CD8 T cell can attack the tumor and gain benefit through the tumor regression.⁴⁷ The number of DC that required to stimulate a potent antitumor immune response is about $0.3-3 \times 10^6$ DC per vaccine).^{48,49} DC administrated by subcutaneous or intradermal

injection nearby peripheral lymph nodes, by intralymphatic or direct intranodal injection.⁵⁰ Once stimulated by an activating stimulus, they undergo maturation and migrate to lymphoid organs where they activate several effector cells of the immune system, primarily T and B-cells.⁵¹⁻⁵³

CASE REPORT

A 52-year-old woman admitted to RSPAD Gatot Soebroto Hospital Jakarta with a case of GBM. Before established as a GBM, the patient was diagnosed with a hemorrhagic stroke. The patient had already had a craniotomy at a hospital in Surabaya to evacuate the blood. When the patient arrived at RSPAD, a series of examinations was performed on the patient. EEG in August 2016 revealed abnormal EEF with the epileptiform wave in the front right temporal. A brain MRI examination in August 2016 resulted as a prominent calcified mass with bleeding component in right thalamus, bilateral mastoiditis, and bone defect in the right temporoparietal region due to past surgery. A series of laboratory examination was also undergone in this patient, with a result of mild anemia.

In 2017, the patient admitted again in the hospital. Chest x-ray performed in August 2017 showed the infiltrates in bilateral perihilar and left pericardium, with differential diagnosis of pneumonia. Another examination was conducted to identify the patient underline disease such as frozen section procedure in August 2017 by a pathologist which resulted as glioma grade III/IV. A histopathology test in August 2017 at the RSPAD Pathology Laboratory confirmed GBM. EGFR (Epidermal Growth Factor Receptor) immunohistochemistry test was 2+. In the same month, an MGMT promoter methylation test presented a methylated status. Tumor percentage was approximately 60%, and the clinical relevance for this test procedure was positive. Partial MGMT promoter methylation has been associated with superior overall survival in anaplastic astrocytoma and anaplastic oligoastrocytoma patients when treated with temozolomide.

Another series of brain MRI with contrast performed in August 2017 showed a solid-cystic mass which was suggested as a malignancy with necrotic component and intratumoral bleeding with the size of 4.5x5x4.7 cm (AP-LL-CC) at the right thalamus. It pressured the right internal capsules, narrowing the right lateral ventricle, 3rd ventricle and causing subfalcine herniation to the left as far of ± 1.5 cm and compelling right side mesencephalon causing uncal herniation. Those presentations confirmed the diagnosis of high-grade gliomas (glioblastoma multiforme).

Another series of brain MRI was performed in

October 2017. It showed solid malignant neoplasm mixed with cystic hypervascular with bleeding and intratumoral necrotic in right basal ganglia, right thalamus, right mesencephalon pressuring right internal capsule, narrowing right lateral ventricle, third ventricle, and causing subfalcine herniation to the left as far as 2 cm and right side uncal herniation. VP shunt attached with the distal tip in left lateral ventricle, VP shunt fully functional, confirmed as GBM. The tumor mass is getting more extensive as a result in August 2017. The patient also conducted an eye examination such as OCT (Optical Coherence Tomography) to inspect the problem with the patient visual acuity in October 2017. The test revealed a result as macular detachment.

The patient first underwent a craniotomy for tumor resection procedure in August 2017. This surgical approach not only targeting to eliminate the tumor tissues but also to retrieve the tumor tissues for pathology examination reason. There is a series of tissue examination of this patient confirmed as GBM. After the surgical approach, this patient also took for radiotherapy and chemotherapy as further treatment. The patient was treated with TheraCIM (Nimotuzumab) and Termodal (Temozolomide) for chemotherapy purpose. Besides the common chemotherapy delivery method, the patient also got an interventional procedure, TACI (Trans Arterial Chemo Infusion). After all the conventional treatment strategies of GBM, the patient was advised completing the new approach of GBM therapy, immunotherapy. This treatment method was initiated in Indonesia Army Cell Cure Center accompanied by Medical Consulting for Cell

Therapy GmbH, Germany.

In this case, the immunotherapy method which chose for this patient were DC vaccines therapy. In DC vaccines therapy, the blood was collected, and then the monocytes were separated from other blood component and “programmed” as DC vaccines. On the 7th day, DC vaccines were then injected intradermally to the patient.

DC vaccines therapy has several specifications, such as the number of viable cells which measured by cell counter, suitability with flowcytometry specifications, have specific morphology of dendritic cells, and the environmental monitoring must be within particular limits. These criteria must be fulfilled before DC vaccines are injected into the patient. In this case, the viable cells of the patient were 1.03×10^7 and suitable with the DC vaccines therapy specification.

DISCUSSION

Brain tumors often bring a piece of bad news to the patient and their families. It is not only the known short survival rate and debilitating nature to the patient quality of life but also the limitation of a treatment option that may give more stress to the patient physical and mental condition. GBM in Indonesia is still rarely reported, even though the treatment strategies of this case in Indonesia already caught up with the most widely known procedure in the world. The need to increase the patient quality of life is still a challenge to the medical professionals in this country. In this occasion, the authors reported a case of GBM in a 52-year-old female who suffers from weakened left extremities and left visual impairments.

As mentioned above, the patient already underwent a series of examination which led to an established diagnosis of GBM. The previous cerebral hemorrhage caused by the intratumoral hemorrhage (ITH). There is 33% of ITH is derived from GBM.⁵⁴ The etiology of ITH is still unknown, but several theories of how this bleeding formed have emerged. Several of them were the bleeding in GBM can occur when large blood vessels are invaded by the tumor growth which eventually drives a weakening and breakdown of the blood vessel walls.^{55,56} Another theory also explained that the weak tumor vessels might not have joined the glial meshwork appropriately which then resulted in decreased resistance power to the trimming forces of the brain itself.^{55,57-59}

Endothelial proliferation process with consecutive occlusion of the blood lumen or occurrence of intratumoral arteriovenous fistulae is another alternative etiology of intratumoral bleeding.^{55,60} In resolving the hemorrhage problem,

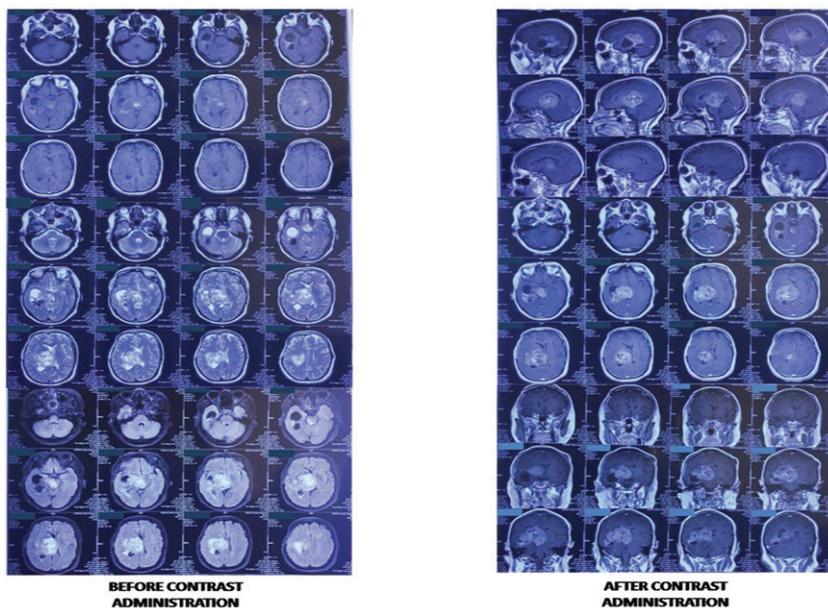


Image 1. Brain MRI results before and after contrast administration.

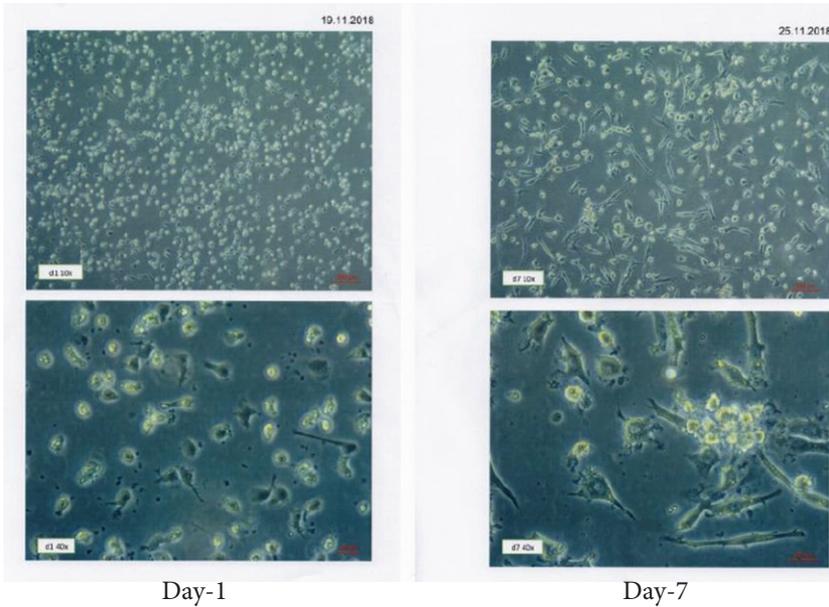


Image 2. Dendritic cells on day-1 and day-7 (Harvest Day)

the doctors decide to conduct a craniotomy to evacuate the blood clot. Several conservative treatment strategies such as radiotherapy and systemic chemotherapy already performed on this patient. Interventional procedures such as TACI was also performed on this patient to increase the chemotherapy drugs efficacy due to the limitation of conservative drugs delivery method into the brain environment. After going through all these conservative strategies, immunotherapy was chosen as the last point for this case, the patient then agreed to all protocols needed to cultivate the patient own immune cells. Indeed, the patient monocytes are collected and then are cultured for at least 7 days. After 7 days, the cultured cells will be injected right back into the patient body intradermally as the best way to administer the vaccines. The clinical condition of a patient had been proved to be better and also already surpassed the average survival rate of GBM.

CONCLUSION

Immunotherapy or especially DC vaccines therapy can be the next treatment of choice for patients suffering GBM.

LIMITATION

There is some limitation to this study that the authors would like to encourage another researcher or medical professionals to expand the possibilities of this new approach by working together with the author's facility.

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