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Controversies in Clinical Trials of Cancer Vaccines for Glioblastoma

Mizuhiko Terasaki[1*], Kenta Murotani[2], Yoshitaka Narita[3], Ryo Nishikawa[4], Tetsuro Sasada[5], Akira Yamada[5,6], Kyogo Itoh[5] and Motohiro Morioka[1]

[1]Department of Neurosurgery, Kurume University School of Medicine, Fukuoka
[2]Translational Research Informatics Centre, Foundation of Biomedical Research and Innovation, Kobe
[3]Neurosurgery Division, National Cancer Centre Hospital, Tokyo
[4]Department of Neurosurgery, Saitama Medical University International Medical Centre, Saitama
[5]Department of Immunology, Kurume University School of Medicine, Fukuoka
[6]Research Centre for Innovative Cancer Therapy, Fukuoka, Japan

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Glioblastoma multiforme (GBM), the most common primary brain tumour, continues to have a dismal prognosis. The standard initial treatment for GBM is surgical resection along with postoperative adjuvant therapy, including temozolomide, concomitant with 60 Gy of radiation therapy (RT) [1]. However, most patients eventually relapse and long-term survival remains elusive [2,3]. Thus, novel therapeutic modalities for GBM are being explored, and different types of immune-mediated approaches have been preclinically and clinically evaluated in phase I and II trials [4]. However, these GBM clinical trials face significant limitations in terms of their assessment of tumour progression and protocol setting. A critical and comprehensive review of how GBM trials should be conducted is required with a focus on how progression can be defined and clinical benefits can be evaluated following the administration of cancer vaccines.

Limitations of the Conventional Tumour Progression Criteria

In current clinical trials of therapies for solid Tumours, cessation of treatment is recommended once "progressive disease" (PD) is detected according to the WHO or response evaluation criteria in solid Tumours (RECIST) criteria. In the WHO criteria, PD is defined as at least a 25% increase in the sum of the products of the two largest perpendicular diameters (SPD) compared with nadir and/or unequivocal progression of non-index lesions and/or the appearance of new lesions [5]. In the RECIST criteria, a 20% increase is defined as PD [6]. Criteria developed by Macdonald and colleagues in 1990 have also been used for assessing the anti-Tumour responses of gliomas [7]. These criteria are based on the two-dimensional WHO response criteria and mark the transition from a subjective interpretation of clinical and radiologic changes to a more objective evaluation. Other factors, such as the use of steroids and changes in neurologic status, are also included in the response assessment. Although they are widely accepted, a number of groups have reported a few limitations of these criteria [8-10]. Clinical evidences indicate that the traditional Macdonald's criteria may not be sufficient for completely characterizing responses in the new era of targeted therapies. Thus, ideal progression criteria that can comprehensively describe all patterns of anti-Tumour responses to cancer vaccines for gliomas remain to be developed.

New systematic criteria designated "immune-related response criteria" for describing additional response patterns observed with immunotherapies that cannot be assessed by the traditional RECIST or WHO criteria have recently been defined [11]. In these new criteria, progression is defined as ≥ 25% increase in Tumour burden compared with nadir at two consecutive time points at least 4 weeks apart in the absence of rapid clinical deterioration. However, these novel criteria may also be of limited value for assessing the anti-Tumour responses of gliomas, as explained below.

Tumour Size Threshold for Defining PD

Tumours with enhancement are defined as PD when the changes in the enhancing areas reach 25% according to Macdonald's criteria. However, whether it is appropriate to define a ≥ 25% increase in Tumour size as "PD" remains unknown. In fact, this issue was raised by our retrospective analysis of the personalized peptide ITK-1 vaccine trial for recurrent GBM, where a 54% increase according to the WHO criteria or a 43% increase according to the RECIST criteria was predictive of a high mortality with a sensitivity of 69% (95% confidence interval: 42%-87%) and 85% (58%-96%), respectively (Figures 1A and 1B). Our experience suggests that the Tumour size threshold for defining PD when evaluating the efficacy of cancer vaccines remains to be carefully determined.

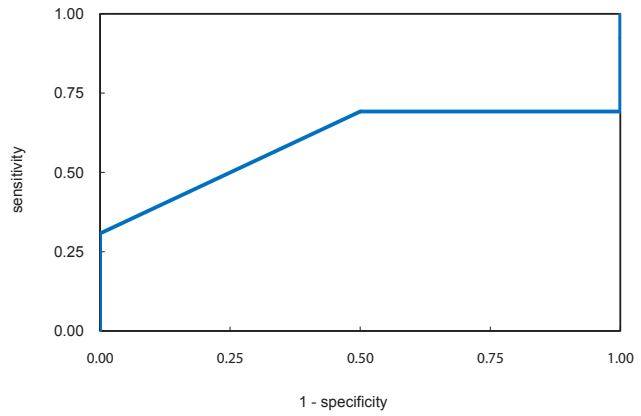

Figure 1a: ROC curve of increasing rate of tumor burden predicting mortality at progression according to the WHO criteria. The area under the ROC curve was 0.69 (95% CI: 0.43, 0.95). Increase in the SPD of at least 54% is predictive of mortality at progression with a sensitivity of 67% (42%, 87%) and a specificity of 50% (9%, 91%).

***Corresponding author:** Mizuhiko Terasaki, Department of Neurosurgery, Kurume University School of Medicine, 67 Asahi-machi, Kurume, Fukuoka 830-0011, Japan, Tel: +81-942-35-3311; Fax: 81-942-38-8179; E-mail: jintara@med.kurume-u.ac.jp

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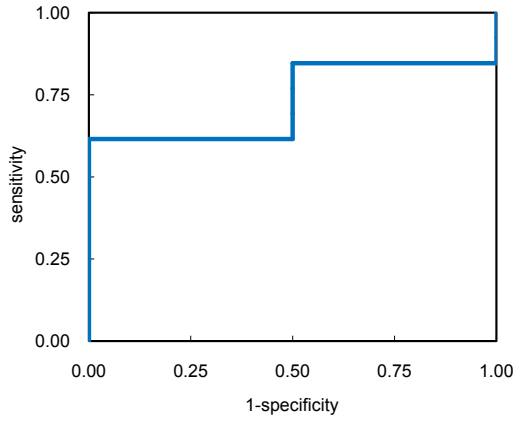

Figure 1b: ROC curve of increasing rate of tumor burden predicting mortality at progression according to the RECIST criteria. The area under the ROC curve was 0.73 (95% CI: 0.42, 1.00). Increases in the largest perpendicular diameters of at least 43% are predictive of mortality at progression with a sensitivity of 85% (58%, 96%) and a specificity of 50% (9%, 91%).

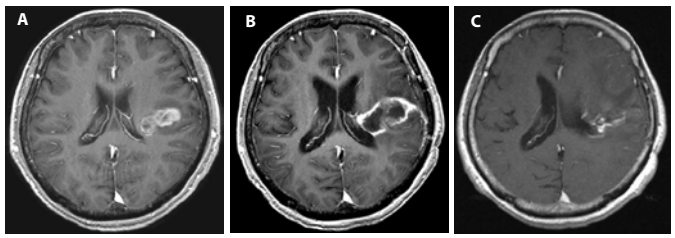

Figure 2: Example of pseudoprogression after vaccination.

(A) T1-weighted contrast-enhanced magnetic resonance image (MRI) from a 59-year-old patient with biopsy-proven glioblastoma before vaccination.

(B) Eight weeks after vaccination, a significant increase in contrast enhancement was shown.

(C) On a follow-up MRI 24 weeks later, a significant reduction was observed in the enhancing lesions.

Controversy Evaluating Enhancing Lesions

Tumour enhancement has been assessed based on the extent of Tumour-occupying lesions when evaluating Tumour size. However, considering that clinical trials of cancer vaccines for gliomas have been attempted in patients at various stages and with various conditions of disease, tumour enhancement may be influenced by not only cancer cell occupation but also by several other factors, including postsurgical changes, disruption of the blood-brain barrier, inflammation, radiation necrosis, and use of corticosteroids [12-17]. These changes in enhancing areas are not always directly correlated with those of Tumour-occupying lesions. Stable disease (SD) in the enhancing areas might be considered an indicator of significant therapeutic effects in cancer vaccine trials [18]. For example, it is possible that enhancement within Tumours may be, at least in part, attributed to autoimmune responses and/or brain inflammation caused by systemic immunization [4].

Tumour Regression after Apparent PD

Clinical studies of cancer vaccines have in certain cases shown that initial induction of SD or PD is followed by subsequent Tumour regression, raising concerns about evaluation of anti-Tumour responses using the WHO or RECIST criteria [11,19]. Such radiological increases in Tumour volumes that precede beneficial clinical responses in patients administered cancer vaccines may be attributed to either continued Tumour growth until sufficient anti-Tumour activity develops, or to transient infiltration of immune cells. In addition, transient increases in enhancement without actual Tumour progression, known as "pseudo progression", have been reported in multiple studies of immunotherapeutic agents [20,21]. For example, in our previous cancer vaccine trial, significant clinical effects after 12 weeks, and in certain cases even after 24 weeks, were observed in a subset of patients with apparent PD according to the classical progression criteria (Figures 2A, 2B and 2C) [22]. Considering the fact that follow-up observations cannot be mandated in patients with PD in most clinical trial protocols, the actual number of patients with beneficial clinical responses after PD may be underestimated. This could limit the value of progression-free survival as a primary end point in cancer vaccine trials.

Collectively, clinical development of cancer vaccines has been hampered by the absence of ideal progression criteria that can comprehensively describe all patterns of anti-Tumour response. Establishment of specific guidelines for classifying Tumour progression to evaluate anti-Tumour activities remains an urgent issue in relation to cancer vaccine trials for gliomas.

Overall Survival as a Primary Endpoint in Cancer Vaccine Trials for Gliomas

Since the numbers of patients with high-grade glioma, particularly GBM, are limited, it would be quite difficult to conduct large-scale immunotherapy trials for this disease [4,12]. The number of patients receiving treatments is relatively small in cancer vaccine trials, and the evaluation criteria vary depending on the trial [22-42]. Such large variations in immune-based therapeutic approaches for GBM make direct comparison difficult. Given this situation, the immunotherapy field needs to urgently address what clinical benefits can be detected in such small-scale, limited clinical trials, and how these can be evaluated. One possibility would be to concentrate on evaluating overall survival (OS). Because of a lack of effective treatments for refractory GBM, the effect of a particular treatment on OS may not be influenced by subsequent salvage treatments.

Combination with the Best Recommended Treatment

A novel hypothetical consideration may be combination therapy with additional agents in GBM vaccine trials, which may enhance the clinical effects of cancer vaccines. Recently, concomitant treatments including RT, chemotherapies, and targeted therapies, have been reported to enhance the therapeutic effects of cancer vaccines through multiple immune-related mechanisms (i.e., activation of antigen-presenting cells or cytotoxic T cells and removal of suppressor cells) [43,44]. Several clinical studies have shown that chemotherapies combined with cancer vaccines can have a synergistic effect [44]. Synergistic effects of salvage chemotherapies after therapeutic cancer vaccination were also reported to improve patient survival in two clinical studies of GBM and small cell lung cancer [45,46]. Sampson et al. [47] reported that cancer vaccination after concomitant RT and temozolomide provided a survival advantage of 9 months compared with control patients in a phase II multicenter trial in patients with newly diagnosed GBM. These clinical studies illustrate that cancer vaccines combined with other treatment modalities may provide a valid therapeutic option for GBM. Therefore, the best recommended treatment (BRT) could be combined with chemotherapies and/or radiotherapies but not with best supportive care (BSC) in clinical trials of cancer vaccines for GBM. This will facilitate the occurrence

of synergistic effects, although the appropriate doses and schedules for optimal synergy between chemotherapies and cancer vaccines remain to be determined.

Considering the disease rarity and the limited survival benefit derived from cancer vaccines for GBM, the employment of BRT (but not of BSC), which could synergistically enhance the clinical effects of the cancer vaccines, would be a breakthrough for accelerated development of cancer vaccines. The FDA also supports this type of combination therapy in their guidelines for the development of therapeutic cancer vaccines [48].

Disclosure Statement

No part of this report has been previously presented elsewhere.

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Conflict of Interest

The authors report no potential conflict of interest except for Itoh.

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