Heat Shock Protein Peptide Complex-96 (HSPPC-96) Vaccination for Recurrent Glioblastoma: A Phase II, Single Arm Trial

We would like to thank Dr. Chamberlain for his thoughtful critique of our study and for highlighting the merits and limitations of an autologous heat-shock protein based vaccine for recurrent glioblastoma (GBM). We reported the results of a phase II, single arm trial of a heat shock protein peptide complex -96 (HSPPC 96) vaccine in patients who underwent complete resection of recurrent GBM.

Chamberlain comments on the applicability of this therapy to all patients with recurrent GBM, estimating that only 15% of patients would meet the eligibility criteria of having a complete surgical resection. Although the requirement of repeat surgical resection with the goal of near-total tumor removal is a limitation of nearly all vaccine-based therapies for recurrent GBM, the true rate at which this can be accomplished is much greater than 15%. At most U.S. tertiary care centers, including all four centers contributing to our study, repeat surgical resection at first recurrence of GBM has become standard of care. We previously reported our institutional case series of patients undergoing repeat surgical resection for GBM, in which we demonstrated complete resection was attained in over 50% of patients regardless of the extent of resection at initial operation.[1] Additionally, we demonstrated that increased extent of resection at recurrence could improve overall survival, supporting the rationale for repeat resection.[1] Similar rates of complete resection at recurrence have been demonstrated in other large institutional case series.[2,3] With the addition of new surgical technologies, including intra-operative MRI, vital dyes, and the advancement of functional mapping, the ability to obtain safer and more complete resections is constantly increasing. For those patients in whom a complete resection is not achievable, there may still be a role for vaccine therapy. Although most current vaccine trials require a minimal burden of residual disease for enrollment, the rationale for this requirement is theoretical and has not been proven clinically. There may be a role for vaccine-based therapy, possibly in combination with immune modulating drugs, for patients with subtotal resection, and this is an area of current exploration.

Chamberlain also raises concerns regarding the ability to generate vaccine from resected tissue and the delay to administration of the vaccine after surgery. In the study, 13 patients (20%) had insufficient tumor resected to produce vaccine for participation. There has undoubtedly been a learning curve for the procurement of tissue and production of the vaccine over time. Since the early days of the study, we have modified surgical techniques to reduce tissue loss and improved manufacturing practices to increase the vaccine yield. Among the later patients enrolled in the study and the subsequent randomized phase II trial of the HSPPC-96 vaccine with or without bevacizumab, we have rarely encountered the problem of insufficient tumor to generate vaccine. Additionally, the manufacturing time for the vaccine is only 16 days, including required time for quality assurance. In the reported study, there was a required post-resection delay of 4 weeks prior to vaccine administration. The purpose of this delay was to allow recovery from surgery and weaning of immunosuppressive post-operative steroids. The delay was predetermined at the time of study design but could be shortened in the future with appropriate rationale.

Finally, Chamberlain comments that the progression-free survival outcomes reported in the trial are not significantly better than those observed with conventional salvage therapy, such as bevacizumab. The primary endpoint of the trial was designed to evaluate overall survival because of the mechanism of action of vaccine-based therapy and the difficulty of assessing true progression. As most patients will not have tissue confirmation at second progression, the determination of progression is largely based on imaging. Differentiating between true progression and pseudoprogression can be difficult, particularly in patients receiving a vaccine that is expected to result in an intra-tumoral inflammatory response and increased contrast enhancement on imaging. By comparison, bevacizumab is known to decrease contrast enhancement and may mask early progression. Therefore, a radiographic comparison of progression between bevacizumab and vaccine-based therapies may overestimate progression-free survival in patients receiving bevacizumab and underestimate progression-free survival in patients receiving vaccine. To ensure that an unequivocal measure of response was assessed, overall survival was selected as the primary endpoint. Additionally, unlike conventional therapies that are only effective during administration, vaccines generate immunologic memory and may continue to have beneficial effects on survival even after progression. Therefore, the only true measure of efficacy is overall survival. When assessing this endpoint, median overall survival from intervention in our study was 42 weeks. Although the trial was single armed, making a direct comparison of efficacy against conventional therapies impossible, the results suggest that further investigation in a randomized controlled trial is warranted.

Immunotherapy remains the most likely adjuvant treatment to effectively target gliomas with minimal toxicity. The introduction of immunomodulatory agents such as anti-CTLA-4, anti-PD1, and anti-PD-L1 antibodies now provides a new pathway to potentiate the immune response elicited by tumor vaccines, and overcome local and systemic immunosuppression in glioma patients. We are grateful to Dr. Chamberlain for asking important questions regarding our study, as well as other studies over the years.[4–14] The answers to most of these questions can only come from thoughtfully designed, randomized clinical trials that test the experimental agents against standard therapies. Currently, the largest randomized trial for a brain tumor vaccine ever initiated by the National Cancer Institute is accruing patients through the Alliance for Clinical Trials in Oncology cooperative group with the endorsement of RTOG. This 3-arm trial will assess survival in recurrent GBM patients receiving the HSPPC-96 vaccine with bevacizumab vs. patients receiving bevacizumab alone vs. patients receiving the vaccine alone followed by bevacizumab at progression. We anticipate the results of this trial to definitively answer the role of vaccine-based therapy in the treatment of patients with recurrent GBM.

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