Author’s response to reviews

Title: Combination of anti-PD-1 therapy and stereotactic radiosurgery for a gastric cancer patient with brain metastasis: A case report

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Author’s response to reviews:

EDITOR COMMENTS

#1: Please provide more information on patient outcome, i.e. did the presented neurological deficit improve after therapy? What is the follow-up time on the patient? Is the patient still alive? For how long following the treatment?

Answer: The neurological symptoms improved and his headaches no longer occurred after only one injection of pembrolizumab. Follow-up physical examination after treatment revealed grade 3 motor weakness in his right lower limb and grade 4 motor weakness in his upper limb. Although a new brain lesion developed after 7 months of pembrolizumab treatment, his neurological symptoms and signs were not aggravated and he is being treated with systemic chemotherapy and pembrolizumab. The patient is currently still alive and in fair general condition 26 months after initial diagnosis. We have added this information to the manuscript.

#2: Also, please elaborate on the mechanism of action in anti PD1 therapy in the context of gastric cancer metastasis in the introduction.

Answer: PD-1 is a negative co-stimulatory receptor expressed mainly on activated T cells, and downregulates excessive immune responses by binding to its ligands, PD-L1 and PD-L2. PD-L1 is constitutively expressed in various tissues and several kinds of malignancies, including gastric
cancer. Binding of PD-1 to PD-L1 inhibits effector T-cell function, thus resulting in suppression of antitumor response and neoplastic growth. Several studies suggested that PD-L1 expression is significantly upregulated following Helicobacter pylori infection and that the resulting decrease in T-cell proliferation can be reversed with anti-PD-L1 antibodies. PD-L1 overexpression was observed in more than 40% of human gastric cancer samples and has been associated with a poor prognosis in several studies. We have added this information to the Introduction.

#3: In addition, the discussion/conclusion section needs to clearly state the limitations of the retrospective case study.

Answer: We have stated the limitations of the retrospective case study.

REVIEWER COMMENTS

Reviewer #1 Federico Ampil:

COMMENT: I believe your subject matter is important because of the dismal results (mean/median survival of 2 months) seen in the two small series of patients (from your referenced reports 1 and 5) reported in the literature.

COMMENT: You need to provide more details on patient outcome after treatment (i.e., did the presented neurological deficit improve after therapy? What is the follow-up time on the patient? Is the patient still alive? For how long following the treatment?)

Answer: PD-1 is a negative co-stimulatory receptor expressed mainly on activated T cells, and downregulates excessive immune responses by binding to its ligands, PD-L1 and PD-L2. PD-L1 is constitutively expressed in various tissues and several kinds of malignancies, including gastric cancer. Binding of PD-1 to PD-L1 inhibits effector T-cell function, thus resulting in suppression of antitumor response and neoplastic growth. Several studies suggested that PD-L1 expression is significantly upregulated following Helicobacter pylori infection and that the resulting decrease in T-cell proliferation can be reversed with anti-PD-L1 antibodies. PD-L1 overexpression was observed in more than 40% of human gastric cancer samples and has been associated with a poor prognosis in several studies. We added this information to the Introduction.

COMMENT: In my opinion, more elaboration of the background information on "anti-PD-1 therapy" might be in order (how it works on the biological level).

Answer: PD-1 is a negative co-stimulatory receptor expressed mainly on activated T cells, and downregulates excessive immune responses by binding to its ligands, PD-L1 and PD-L2. PD-L1
is constitutively expressed in various tissues and several kinds of malignancies, including gastric cancer. Binding of PD-1 to PD-L1 inhibits effector T-cell function, thus resulting in suppression of antitumor response and neoplastic growth. Several studies suggested that PD-L1 expression is significantly upregulated following Helicobacter pylori infection and that the resulting decrease in T-cell proliferation can be reversed with anti-PD-L1 antibodies. PD-L1 overexpression was observed in more than 40% of human gastric cancer samples and has been associated with a poor prognosis in several studies. We added this information to the Introduction.

COMMENT: As you know, it is always difficult to declare the worth of any new treatment scheme based on a retrospective single case study.

Response: We stated the limitations of the retrospective case study.

Reviewer #2 Samuel Chao:

COMMENT: This is a well-written case report. The response of the disease in response to pembrolizumab following brain SRS is suggestive of synergistic effect as the authors mentioned. Given this case report is of gastric cancer, this is unique.

Response: Thank you very much for your good comments.