

In reply: Tumor-associated lymphocytes expanded ex vivo from malignant ascites

We do appreciate Dr. Seong's comments about our recently published article on the proliferation of regulatory T (Treg) cells in ex vivo expanded ascitic fluid from ovarian cancer, and we would like to address two points that Dr. Seong has made.

Dr. Seong's first comment was that the higher ex vivo expansion of Treg cells in recurrent ovarian cancer might be related to the depletion of Treg cells which had been induced by previous chemotherapy. Although chemotherapy is usually considered immunosuppressive, some chemotherapeutic agents activate an anticancer immunity. Beyer et al. have reported that in patients with chronic lymphocytic leukemia (CLL), treatment with fludarabine and cyclophosphamide reduced Treg cell numbers and inhibited CD4⁺CD25⁺ Treg cell function.¹ Recently, Aruga et al.² proved that low number of tumor-infiltrating Foxp3⁺ cells during primary systemic chemotherapy correlated with favorable anti-tumor response in patients with breast cancer. However, in contrast, Correale et al.³ reported that a favorable outcome was observed in colon cancer patients with autoimmunity signs, increase of central memory T cells and decrease of Treg cells in the peripheral blood. In their results, higher Foxp3⁺ Treg tumor infiltration score was a favorable prognostic factor in colon cancer patients undergoing chemo or chemoimmunotherapy. Shimizu et al.⁴ reported that tumor-infiltrating Foxp3⁺ Treg cells were correlated with recurrence in resected non-small cell lung cancer by cyclooxygenase-2 expression. The recurrence free survival of patients with tumors containing ≥ 3 Foxp3-positive cells was significantly worse than that of patients with tumors containing < 3 Foxp3-positive cells. Considering these diverse results, the depletion of Treg cells induced by chemotherapy and their influence to prognosis should be investigated to be proven. Actually, in our results, there is no significant difference of Treg cells proportion between primary and recurrent cases before ex vivo expansion, as mentioned within the article (0.32 ± 0.12 vs. 0.33 ± 0.17). Dr. Seong's another comment was about the diagnostic criteria for recurrent ovarian cancer. However, this seems to be misled by unclear expression. The median number of previous chemotherapy sessions in the recurrent ovarian cancer, in Table 1, means different regimens, not cycles of one regimen. The authors selected cases with recurrent ovarian cancer, among patients received standard

treatment of advanced ovarian cancer.

In conclusion, we performed this study to ascertain whether tumor-associated lymphocytes (TAL) in malignant ascites were appropriate to a source for adoptive cellular immunotherapy in ovarian cancer. We believe that the way performing this study was valid and gave us the answer to our question, even though there are "more questions than answers" on the topic of Treg cells.

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