Peer Review File

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Reviewer A

A case of pseudomyxoma peritonei successfully treated with trifluridine/tipiracil (TAS-102) and bevacizumab after palliative debulking surgery

Authors claimed that they have isolated a new therapeutic solution to treat PMP, using chemotherapy and antiangiogenic drug.

Comment 1: Major limit of the paper:

- If nothings append after 2 years of an incomplete cytoreductive surgery for a low grade PMP, it is difficult to be certain that the treatment had an effect. The clinical situation of non progression of the disease is observed in case of no treatment, as usually I perform in that situation.

Reply 1:

Thank you for your advice.

First, we consider this case as a **high-grade appendiceal mucinous neoplasm (HAMN)** accompanied by PMP as written in line 79-80.

HAMN is a new concept established in 2016, so we added the detail histopathological characteristics of HAMN in discussion part (106-110 in discussion).

We also consider this case as a kind of unresectable PMP treated with palliative systemic chemotherapy, because the residual disease was massive (CCR3). We added "CCR3" in the line 78.

For patients with recurrent, or unresectable, PMP treated with palliative systemic chemotherapy, PFS is thought to be from 6 to 8 months, and OS ranged from 26 to 61 months. We added this content in line 119-121 in discussion.

Second, as we showed in his clinical course in figure 3, CEA level rapidly elevated during chemotherapy with agents other than TAS102 plus bevacizumab. Moreover, a small amount of mucinous pleural effusion appeared before starting the chemotherapy with TAS-102 plus bevacizumab.

Therefore, the combination chemotherapy with TAS-102 and bevacizumab, whose PFS was more than 2 years, was quite beneficial for this patient, even though his best response was SD. Just observation was considered too risky for this setting.

Changes in the text:

① We added the sentences “The histopathological characteristics of HAMN includes, at least focally, loss of polarity with full-thickness nuclear stratification, nuclei that are enlarged, markedly hyperchromatic or vesicular, prominent nucleoli, numerous or atypical mitotic figures, or cribriform growth (2). Some of these characteristics were demonstrated in our case (figure 2A).” in lines106-110 in discussion.

② We added “CCR3” in the line 78.

③ We added the sentence “For patients with recurrent, or unresectable, PMP treated with palliative systemic chemotherapy, PFS ranged from 6 to 8 months, and OS ranged from 26 to 61 months (2).” in 119-121 in discussion.

Comment 2:

So we need to have a pathological high quality report including second lecture and pictures reported with explanation using arrow or identified abnormality.

Reply 2:

Thank you for your important opinion. As you pointed out, it was difficult to fully understand the characteristics of HAMN with the former picture. We changed pictures and added arrows to express important points. We also added the detail histopathological characteristics of HAMN in discussion part (106-110 in discussion) as above.

Changes in the figure and figure legends:

We changed the picture of Figure 2A (x200). We also used arrows to show important parts. The new figure legend of figure 2 are as below. (line 226-231)

Figure 2. Histopathology of the primary lesion (A, 200×) and disseminated lesion (B, 100×). A) Papillary or dendritic proliferation with swelling, enlargement, and stratification of the nucleus (arrow), equivalent to high-grade appendiceal mucinous neoplasm. B) Tumor epithelium is demonstrated at the margins of mucus nodules (arrow). Abundant fragments of neoplastic mucinous epithelium are seen floating in the mucus (arrow).

Comment 3: Minor point

The initial PCI and post cytoreductive PCI had to be give by the authors.

Response

Unfortunately, we have not evaluated PCI. However, the residual tumor was massive and CCR was 3. We added “CCR3” in the line 78 as above.

Comment 4:

The reference of paper associating PMP and antiangiogenic drugs could be interesting for readers/

Successful antiangiogenic combination therapy for pseudomyxoma peritonei with bevacizumab and capecitabine.
Sun WL, Hutarew G, Gradl J, Gratzl M, Denz H, Fiegl M. Cancer Biol Ther. 2009 Aug;8(15):1459-62.

Orthotopic animal model of pseudomyxoma peritonei: An in vivo model to test anti-angiogenic drug effects.
Dohan A, Lousquy R, Eveno C, Goere D, Broqueres-You D, Kaci R, Lehmann-Che J, Launay JM, Soyer P, Bonnin P, Pocard M. Am J Pathol. 2014 Jul;184(7):1920-9.

Improved Survival with Anti-VEGF Therapy in the Treatment of Unresectable Appendiceal Epithelial Neoplasms.
Choe JH, Overman MJ, Fournier KF, Royal RE, Ohinata A, Rafeeq S, Beaty K, Phillips JK, Wolff RA, Mansfield PF, Eng C. Ann Surg Oncol. 2015 Aug;22(8):2578-84.

GNAS mutations as prognostic biomarker in patients with relapsed peritoneal pseudomyxoma receiving metronomic capecitabine and bevacizumab: a clinical and translational study.
Pietrantonio F, Berenato R, Maggi C, Caporale M, Milione M, Perrone F, Tamborini E, Baratti D, Kusamura S, Mariani L, Niger M, Mennitto A, Gloghini A, Bossi I, Settanni G, Busico A, Bagnoli PF, Di Bartolomeo M, Deraco M, de Braud F. J Transl Med. 2016 May 6;14(1):125.

Reply 4:

Thank you for your valuable suggestion. Two of four articles you mentioned was already cited in our case report.

We appreciate for your important suggestions.
Sincerely.

Reviewer B

Comment 1:

Interesting clinical case. Could be illustrative for future challenges. To my Knowledge the conclusion must be modified, including in abstract:
(SUGGESTION IN CAPITAL LETTER)

"Combination chemotherapy comprising TAS-102 and bevacizumab IN PATIENTS WITH PALLIATIVE DEBULKING could be a useful option for patients with high-grade mucinous appendiceal neoplasm and high-grade pseudomyxoma peritonei.

Reply1:

Thank you for your valuable suggestion.
We added the sentence “In conclusion, combination chemotherapy comprising TAS-102 and bevacizumab IN PATIENTS WITH PALLIATIVE DEBULKING could be a useful option for patients with high-grade mucinous appendiceal neoplasm and high-grade pseudomyxoma peritonei.” at the last part of the abstract. We also used the sentence you suggested in discussion.

Changes in the text:

We deleted the last part of the abstract and inserted the sentence “In conclusion, combination chemotherapy comprising TAS-102 and bevacizumab IN PATIENTS WITH PALLIATIVE DEBULKING could be a useful option for patients with high-grade mucinous appendiceal neoplasm and high-grade pseudomyxoma peritonei.” in line 44-46 in the abstract.

We also changed the last part of the discussion and added the sentence “In conclusion, combination chemotherapy comprising TAS-102 and bevacizumab IN PATIENTS WITH PALLIATIVE DEBULKING could be a useful option for patients with high-grade mucinous appendiceal neoplasm and high-grade pseudomyxoma peritonei.” in line 159-161 in discussion.

We appreciate for your important comments and suggestion.
Sincerely.