Peer Review File

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Reviewer A

General Comments:

Yang et al described an update on S-1: a potential monotherapy and combination treatment option for advanced non-small-cell lung cancer: a narrative review. The search term and period of the search are clear and well described. Hereby some minor revision that will straighten the review.

Comment 1: Introduction - Please attach the Narrative Review reporting checklist (available at https:..). It is missing in the introduction.

Reply 1: We gratefully appreciated your comment. We have modified our text as advised. Thanks again for your valuable comment.

Changes in the text:

"We present this article in accordance with the Narrative Review reporting checklist (available at https://tcr.amegroups.com/article/view/10.21037/tcr-23-2019/rc)."(line 72-74).

Comment 2: Introduction - It is not clear from the introduction session in which way S-1 can be used in NSCLC patients. Which stadium? Which line of treatment? In what way is this treatment filling the gap in which NSCLC patients are treated better? It is becoming clear in the rest of the review, but state it also brief in your introduction.

Reply 2: We gratefully appreciated your comment. We have enriched S-1 in the introduction part as advised. Thanks again for your valuable comment.

Changes in the text:

"S-1 was approved in Japan in 2004 for the treatment of non-small cell lung cancer. S-1 monotherapy or combination therapy has also shown good anti-tumor activity in advanced NSCLC as first-line, second-line, or later-line treatments. In late-stage NSCLC patients with no driver gene mutations, weakened physical functions, multiple underlying diseases, and high PS scores, which have resulted in limited treatment options, S-1 could fill the gap."(line 66-70).

Comment 3: Conclusion and future perspectives - Is there an advice you can give to physicians which NSCLC patients benefit the most?

Reply 3: We gratefully appreciated your comment. We have advised physicians which NSCLC patients benefit the most in the conclusion and future perspectives part as advised. Thanks again for your valuable comment.

Changes in the text:

"In patients with advanced NSCLC with no driver gene mutation, age-related functional decline, multiple underlying diseases, and poor treatment tolerance have resulted in limited treatment options. S-1 has good clinical efficacy and a low incidence of adverse reactions, not only prolonging life but also improving the quality of life for patients, making it a new choice."(line 352-355)

Comment 4: Conclusion and future perspectives - Can you mention new or ongoing trials and there study set up?

Reply 4: We gratefully appreciated your comment. We have added new or ongoing trials in conclusion and future perspectives. Thanks again for your valuable comment.

Changes in the text:

"New researches have explored the S-1 in more detail. A preliminary clinical study conducted by Tanaka et al. explored the efficacy of combination of immunotherapy with S-1 and radiotherapy(1). This study of durvalumab after cisplatin plus S-1 (SP)-based chemoradiotherapy (CRT) found a 1-year PFS of 73%. A phase II clinical study conducted by Yamamoto et al. explored the frequency of S-1 administration. They found that both alternate-day and daily oral administrations of S-1 were demonstrated to be feasible in elderly patients with completely resected NSCLC(2). S-1's role as a therapeutic approach to advanced NSCLC will be further defined by results of ongoing and future trials."(line 356-361)

Reviewer B

General Comments:

This is a well-written review with systematic database search and rigorous summary.

Comment 1: What is the current approval status of S-1 across the world? As far as I know, it is not approve by US FDA which may limit its usage.

Reply 1: We gratefully appreciated your comment. Japan approved S-1 in 2004 to treat non-small cell lung cancer, but other countries have not approved it. However, with the increasing number of clinical studies, S-1 is still very promising in the future due to its low price, good therapeutic effect, and few adverse reactions. Thanks again for your valuable comment.

Comment 2: For table 2~4, could the authors add a column of where are the trials conducted and another column summaries the conclusion of each trial listed?

Reply 2: We gratefully appreciated your comment. We have modified our table as advised. Thanks again for your valuable comment.

Changes in the table:

Table 2. First-line S-1 Monotherapy or in combination with other agents.

Regimen	Region	Conclusion
S-1	Japan	In elderly patients with previously untreated advanced NSCLC, S-1 appears to be well tolerated and demonstrates encouraging activity.

S-1	Japan	In elderly patients with previously untreated advanced NSCLC, a 2-week S-1 monotherapy treatment, with a 1-week interval was well tolerated and demonstrated promising efficacy.
S-1 + CDDP	China	Oral S-1 plus cisplatin is an effective and safe first-line regimen for patients with advanced NSCLC.
S-1 + CDDP versus DTX + CDDP	Japan	Oral S-1 plus cisplatin is not inferior to docetaxel plus cisplatin and is better tolerated in patients with advanced NSCLC.
S-1 + CBDCA	Japan	The oral S-1 plus carboplatin regimen seems to be a favorable treatment option.
S-1 + Gem	Japan	The combination of gemcitabine and S-1 may be a promising and feasible regimen in the first-line setting for elderly patients with advanced NSCLC.
S-1 + PTX	Japan	S-1 and paclitaxel showed satisfactory efficacy with mild toxicities in elderly patients with advanced NSCLC.

S-1 + CDDP + Bev f/b Bev	Japan	S-1 plus cisplatin in combination with bevacizumab met the primary endpoint in patients with advanced non-squamous NSCLC. The response rate was anticipated to be high with acceptable toxicities.
S-1 + CDDP + Bev f/b Bev versus MTA + CDDP + Bev f/b Bev	Japan	The combination regimen of S-1 + cisplatin + bevacizumab (SCB) was identified as having a similar activity and tolerability to that of pemetrexed + cisplatin + bevacizumab (PCB) in patients with advanced non-squamous NSCLC.
S-1 + CBDCA + Gefitinib	Japan	Combination chemotherapy with carboplatin, S-1, and gefitinib is efficacious and well tolerated as a first-line treatment in advanced NSCLC patients with activating EGFR mutations.

Table 3. Second-line or Later line treatment S-1 Monotherapy or in combination with other agents

Regimen	Region	Conclusion
S-1	Japan	Alternate-day S-1 administration can be a safe treatment regimen for elderly

		patients with NSCLC.
S-1	Japan	S-1 monotherapy is effective and feasible as a subsequent-line treatment in elderly patients who were previously treated for NSCLC.
S-1 versus DTX	Japan	S-1 is equally as efficacious as docetaxel and offers a treatment option for patients with previously treated advanced NSCLC.
S-1 versus DTX	Japan	S-1 had similar efficacy to docetaxel in patients with previously treated advanced NSCLC.
S-1+DTX	Japan	Docetaxel plus oral S-1 had a lower response rate than anticipated; however, the survival data were encouraging.
S-1+PTX	Japan	S-1 and PTX co-therapy dose and schedule showed satisfactory efficacy, with mild toxicities, in patients with previously treated advanced NSCLC.
DTX+ Bev versus S-1+Bev	Japan	Docetaxel plus bevacizumab (DB) and S-1 plus bevacizumab (SB) produced modest PFS benefits in the second-line treatment of patients with advanced non-squamous NSCLC.

S-1+ Bev	Japan	Although S-1 + bevacizumab (SB) was well tolerated, this combination did not provide any additional benefit in terms of PFS for patients with non-squamous NSCLC after failure of platinum-based chemotherapy.
S-1+ Bev	Japan	The addition of bevacizumab to S-1 was tolerable, but not beneficial for patients with previously treated non-squamous NSCLC.
S-1+ Anlotinib versus Anlotinib	China	Advanced squamous NSCLC patients with higher PS scores still benefit from anlotinib and S-1 combination regimen, even after they failed second-line or later-line systemic treatment.
S-1+ Anlotinib	China	The combination of anlotinib with S-1 in the third- or later-line treatment of stage IV NSCLC shows promising antitumor activity and manageable toxicity in patients with NSCLC.
S-1+ Apatinib	China	Combination of low-dose apatinib and S-1 could be an effective and tolerable choice for advanced NSCLC patients who are unable to benefit from standard treatment.

S-1+ Apatinib	China	Apatinib plus S-1 for advanced solid tumor patients as palliative treatment have a certain efficacy and was relatively safe.
S-1+ Erlotinib	Japan	The combination therapy of erlotinib plus S-1 was not feasible in the EGFR wild-type NSCLC at least and early stopped.

Table 4. S-1 with immunotherapy (Tamura et al., 2019, Japan (60))

	S-1	DTX
Conclusion	Subsequent cytotoxic chemotherapy, especially immediately after nivolumab, has better treatment efficacy than that of regimens without ICI pretreatment.	