Peer Review File

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Reviewer Comments

Reviewer #1
This review tries to present the current evidence for the combined treatment of locally advanced NSCLC with a focus on toxicity.

Comment 1:

- My major concern is the fact that only very limited data are available.
  - The only substantial publication on this topic is the PACIFIC study (NEJM 2017 and 2018), which is extensively summarized under *Consolidative ICB in Unresectable Stage III NSCLC*. The other studies mentioned in this chapter are either published in abstract form only (Hoosier trial) and / or comprise very small numbers of patients (NCT 03285321).
  - As for the concurrent combination of ICB and radio(chemo)therapy practically no data are available, which per se precludes a review. Consistently pages 10 – 12 are written in future tense. Yet a review – per definition – is a sort of text that summarizes evidence that was generated in the past. Listing studies that "will provide" data is not very helpful.

Reply 1: Thank you for your feedback. As the Guest Editor notes, while the PACIFIC trial is well publicized, multiple prospective trials with consolidative or concurrent ICB have recently provided additional published safety data. Recently published phase II trials evaluating CRT and concurrent and consolidative ICB that we have summarized in our review include the phase II DETERRED trial (Lin et al., JTO 2019), phase II NICOLAS with 80 patients (Peters et al., Lung Cancer 2019), and the phase I trial Rutgers trial (Jabbour et al, JAMA Oncology, 2020). These recent publications (and abstracts from other trials presented at ASCO and other major conferences) substantially multiply the available evidence in a space where previously PACIFIC was the only trial of note, and did not provide safety data for concurrent chemoradiation and IO. After PACIFIC, ICB achieved widespread implantation in clinical practice, and it is imperative to review safety data from recently published studies involving ICB in chemoradiation patients in the context of the toxicity profile of PACIFIC, standard chemoradiation (i.e. RTOG 0617 standard dose arm), and trials of targeted agents to confirm this practice is safe with respect to the alternatives. Despite these recent publications, questions regarding the value of combining multiple ICB agents targeting parallel/different pathways, the most effective sequencing of therapy (concurrent ICB, consolidative ICB, or both), and additive toxicities remain. Given how quickly the literature is evolving in this space, we feel that reviewing ongoing trials addressing unanswered questions provides important context for the reader so that they know what to expect on the horizon.

Changes in the Text:

1) Lines 207-209: Until recently, PACIFIC was the only noteworthy publication evaluating chemoradiation and ICB therapy, but multiple prospective trials have recently provided additional published data, and others have reported initial findings in abstract form at major international conferences

2) Lines 357-381: After the PACIFIC trial demonstrated a PFS and OS benefit to maintenance anti PD-L1 therapy after concurrent chemoradiation, standard of care shifted to include consolidative ICB (durvalumab) for unresectable Stage III NSCLC, especially for patients with PD-L1 expression 1% or greater. The benefit of durvalumab largely seems to outweigh the

added risks of toxicity with ICB and has been well-accepted as a new standard. One recent approach has been intensification of consolidative ICB therapy. Overall, addition of single agent consolidative ICB (like PACFIC) leads to acceptably higher rates of mild to moderate immune related toxicity with respect to chemoradiation alone. Rates of more serious G3-4 pneumonitis of 0-5% have been noted with single agent(14,29,34) and certainly appear higher at about 10% with dual agent therapy(32), but overall are similar to the 7% rate of grade 3+ radiation pneumonitis seen with standard dose chemoradiation on RTOG 0617(5). These side effects are generally manageable through corticosteroids and/or discontinuation of therapy(13), but a roughly 1% rate of fatal pneumonitis (G5) has been observed in several studies(14,29). Of note, rates of completion of the full course of ICB in studies with consolidative therapy alone are modest, ranging from 37-49%(14,29)

In terms of concurrent ICB with chemoradiation, a number of phase I/II studies have been published, suggesting the relative safety of the combination, but appear to have slightly increased rates of mild to moderate immune related toxicity with respect to consolidative ICB alone. A 18-20% rate of grade 3+ immune-related toxicity events was seen with concurrent and consolidative ICB on the CINJ 031507 and DETERRED trials(34,35) which was higher than the 3.4% rate seen at the time of initial reporting of the PACIFIC trial(13). Additionally, reported rates of any pneumonitis, ranging from 23-42.5% (33,34) with concurrent and consolidative ICB may be slightly higher than the 10-33% reported rate of pneumonitis with consolidative ICB alone (14,29,32,34). However, rates of grade 3+ pneumonitis of 3-10% (33,34) were relatively similar to 0-5% rates with single agent consolidative ICB alone(14,29,34) and 7% with SD CRT on RTOG 0617(5). The 10% rate of G3+pneumonitis and 5% G5 (one patient) pneumonitis observed in the NICOLAS and CINJ 031507 trials respectively, however, warrants closer evaluation in ongoing phase II/III trials.

3) The citation for Jabbour et al. has been updated to reflect the recent publication in JAMA Oncology as have the reported toxicity rates from that trial.

Comment 2: A minor aspect – although soundly written – is the largely repetitive character of the manuscript. The conclusion is rather an extension of this repetition than a short summary of what the key message of the paper is.

Reply 2: Thank you for your feedback. The key message is that while addition of ICB leads to acceptably higher rates of mild to moderate immune toxicity with respect to chemoradiation, with highest rates seen with more therapy (through either addition of concurrent or dual agent therapy), there is no observed increase in acute esophageal toxicity, and the full pulmonary and cardiac effects of these therapies are not yet known. These are important points, because acute esophageal toxicity and cardiac dose have been linked to inferior overall survival in RTOG 0617. Future randomized phase II/III studies will need to carefully evaluate for these toxicities.

Changes in the Text:

1) Lines 357-381 in the conclusion section have been re-worded/added to more clearly summarize the findings of the reported studies and comparisons to more standard therapies (RTOG 0617 and PACIFIC).

Comment 3:

- Page 2: "(…) poor survival and failed CRT intensification, …" : I agree with the idea that survival in LA-NSCLC patients treated with standard CRT only is still poor. But this is a question of how treatment intensification is carried out since the "failure" can only refer to standard CRT as presented in the RTOG 0617 trial. Yet this ignores the studies with a vast range of alternatively fractionated schemes (CHART, INDAR, Baardwijk JCO 2010, reviewed by Kaster Clin Lung Cancer 2015 or Zehentmayr Thoracic Cancer 2020).

Reply 3: This comment is appreciated. We have edited the text to reflect that RTOG 0617 was a failure in dose escalation with standard fractionation, and provided insights into altered fractionation schemes.

Changes in the Text:

1) Line 39 "However, efforts to improve outcomes through radiation dose escalation with standard fractionation to 74 Gy, or the addition of cetuximab on that trial were unsuccessful.", and deletion in Line 55.

2) Lines 44-55: It is also hypothesized that prolonged overall treatment time (OTT) may have contributed to the failure to improve OS, lending interest to hypofractionated or hyperfractionated regimens that shorten overall treatment duration(7,8). A single arm prospective trial found that hyperfractionated radiation therapy with sequential chemotherapy yielded survival rates comparable to outcomes with concurrent chemoradiation(9). Another randomized prospective trial without chemotherapy found an OS benefit with hyperfractionation compared to conventionally fractionated radiation therapy, without chemotherapy (10). Despite this, hyperfractionation studies with concurrent chemoradiation have not consistently found a significant OS benefit with respect to standard fractionation(7,11). A systematic analysis investigating hypofractionation in stage III NSCLC found no significant correlation between 1-, 2-, and 3-year OS and acute effects BED lesional dose (BED10), but reported an absolute OS benefit of 0.36-0.7% for every 1 Gy increase in BED (8). Thus, dose escalation through hypofractionation or SBRT boost is an active area of investigation.

Reviewer #2

This is a well written review on an important topic. Some detailed thoughts are below:

Comment 1: There is a lot of text summarizing the results of RTOG0617 and PACIFIC. If space is an issue, perhaps these sections could be condensed, given that both studies have been published and well-reviewed by others.

Reply 1: Thank you for this advice. Even with revisions, we are currently below the 6000 word limit for a review article.

Changes in the Text: none

Comment 2: In the section of chemoradiation toxicity without immunotherapy, it is unclear why PARP inhibitors were highlighted, but no other agents like EGFR TKIs. The proton therapy section also feels a bit out of place. This section could probably be reorganized. If targeted/biologic agents are going to be discussed, then the scope should be expanded.

Reply 2: Thank you for your comments. Our goal was to review the safety data for patients receiving IO and CRT particularly in the context of standard chemoRT but also other reasonable alternatives. PARP inhibitors were highlighted as there was recent available data for comparison from trials started shortly before PACIFIC presented its findings. We have also added data from phase II and III trials with EGFR inhibitors in unresectable stage III NSCLC. Additionally, the ongoing LAURA trial in patients with EGFR mutated tumors is reviewed in the ongoing trials section. Regarding RTOG 1308, we feel inclusion in this review is reasonable, because lymphopenia has been associated with impaired PFS and OS in patients receiving immunotherapy for advanced NSCLC, and a reduction in lymphopenia through sparing with protons may improve the efficacy of immunotherapy.

Changes in the Text:

1) Lines 132-151: In the early 2000s, a phase III trial (SWOG 0023, NCT00020709) was conducted evaluating the benefit of maintenance gefitinib, an epidermal growth factor (EGFR) inhibitor, to standard of care concurrent chemoradiation therapy in patients with unknown EGFR mutation status (22). 243 patients were accrued before an unplanned interim analysis found that the gefitinib arm had significantly worse OS, and the study was thus terminated. Patients were treated with cisplatin (50 mg/m^2) and etoposide (50 mg/m^2) chemotherapy concurrent with RT to 61 Gy in 1.8 – 2.0 Gy fractions followed by 3 cycles of docetaxel, and patients with no evidence of progression were randomized to maintenance gefitinib 250 mg/day or placebo. During concurrent RT, a 13% rate of G3+ esophagitis was reported. Additionally, a 7% rate of G3+ pneumonitis was noted after definitive chemoradiation including a 1% rate of fatal pneumonitis. Maintenance gefinitib was associated with a 1% rate of pneumonitis. The results from this trial led to the premature closure of an additional phase II trial (NCT00040794) evaluating gefitinib concurrent with radiation therapy in patients unselected for EGFR mutation status(23). 63 patients were enrolled before trial closure. They received two cycles carboplatin (AUC 6) and paclitaxel (200 mg/m^2) plus gefitinib 250 mg daily. Patients deemed to be "poor risk" by performance status 2 and/or presence of greater than or equal to 5% weight loss then received 66 Gy in 33 fractions with concurrent gefitinib, and patients who did not meet those criteria were considered "good risk" and received concurrent carboplatin (AUC 2) and paclitaxel (50 mg/m^2) in addition to RT and gefitinib at the same dosing. All patients continued on consolidation gefitinib at unchanged dose until disease progression. There were 19% and 31% reported rates of G3+ esophagitis in the "poor" and "good" risk groups, respectively and 15% and 16% rates of pneumonitis or pulmonary infiltrates including one lethal pulmonary event in each arm.
2) Lines 163-169: Additionally, a single institution analysis reported 16% and 0% rates of G3 and G4 acute leukopenia, respectively, with proton therapy for stage III NSCLC(26) which compared favorably to the 25% and 3% rates of G3 and G4 acute leukopenia in the 60 Gy arm without cetuximab on RTOG 0617(6). If proton therapy can minimize reductions in white blood cell counts, it may increase the effectiveness of the immune response associated with concurrent or consolidative ICB, as lymphopenia around the time of immunotherapy delivery has been associated with impaired PFS and OS in locally advanced or metastatic NSCLC(27).

Comment 3: Table 1. Reformat so the column width does not cut words in half.

Reply 3: Thank you for this suggestion. The table format has been adjusted.

Changes in the Text: table formatting was changed.

Comment 4: Table 2. PACIFIC-2 is testing concurrent and consolidation D versus placebo, not just concurrent D vs. placebo? Not sure RTOG1308 really belongs on this list as it is not asking an immunotherapy question.

Reply 4: Thank you for this comment. The PACIFIC-2 table entry has been corrected as mentioned, and RTOG1308 has been removed from the table.

Changes in the Text: The PACIFIC-2 table entry has been corrected to say concurrent and consolidative D, and RTOG1308 has been removed from the table.