TRANSLATIONAL CANCER RESEARCH

Peer Review File

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Reviewer A

The authors present a meta-analysis of RCHOP-14 vs RCHOP-21 in NHL. The novelty of the manuscript is very limited given that some good quality clinical trials have been performed and did not demonstrate superiority of RCHOp-14 over standard of care 21-day cycle. The only potential novelty or value to this study would be for considering the data in patients with iNHL. However, those patients aren't well represented in any of the studies. The authors also include 2 studies in which the tx allocation was by investigator/physician choice - clearly those studies would not merit inclusion into the analysis. Unfortunately, I don't think that there is sufficient novelty or good enough quality analysis to make this manuscript worthy of publication or of interest to readers.

If the authors try to edit the manuscript to improve it, they will also need to ensure revision of the English. I'm not sure what is meant by superordinate (page 5, line 68). The intro briefly mentions PMBL and MCL which are not relevant to the included studies or this study's conclusions.
Reply: The grammatical errors in the sentence have been corrected. Superordinate was changed to superior.

Reviewer B

The authors present a meta-analysis of comparing RCHOP regimens. Please review your article for grammar and proofread.

Line by line comments:

Line 55: ...and they are treated with different chemotherapy regimens...
Line 57-58: Change " be converted" with "transform"
Line 62-63: This should be changed from median survival of NHL to median survival of DLBCL.
Line 63-64: Grammatical error; change "....treatment for DLBCL is..." to "treatment for DLBCL was"
Line 68: Consider changing superordinate to superior
Line 69-70: Consider rewording this sentence.

Line 78: Change the word "proved" to something else. Maybe ...it has been observed that rituximab-based treatment....
Line 84: Change "toxic" to "toxicity"
Line 102-103: The second to last sentence in this paragraph does not make sense. Reword.
Reply: The above grammatical errors have been revised.
103-104: What was the senior referee's qualifications?
Reply: It means expert in this field.
Lines 134-135: For duplicate articles, did you use the most recent update of a data set or the original trial? Some clinical trials have follow-up data, so would be curious if the first or last article on the study were excluded.

Reply: Lines 134-135: For duplicate articles, I used the most recent update of a data set . We carefully read the title and summary, methods to determine whether it belongs to the same CT registration number. If two articles belong to the same clinical trial, the same participant should not be included twice. We chose the newly published one, which can avoid the survival bias caused by insufficient follow-up time.

147-149: You end up biasing your results by including indolent into aggressive lymphomas. Not sure if you would consider splitting them into two separate groups? I cannot tell from your table if most are DLBCL and only 1 trial included had all of NHL (Payandeh2016).

Reply: 147-149: The theme of this paper is aggressive or advanced stage indolent B-cell Non-Hodgkins Lymphoma(NHL) the reason why these two subtypes of lymphoma are put together is that advanced inert lymphoma is aggressive and highly malignant. The final clinical manifestations of these two types of patients are similar, clinical treatment and prognosis are also similar, so we did not group them. Diffuse large B-cell lymphoma (DLBCL) is the most common subtype of aggressive lymphoma, PMBL is a unique subtype of DLBCL. Untreated advanced-stage FL is also an aggressive lymphoma, so the data in the table 1 belong to the same category of diseases.

156: Allocation should not be capitalized.
Reply: It has been modified.
178-179: Do you mean results were not different after categorized by IPI scores?
Reply:YES
179-180: Characterizing by IPI does not dichotomize between indolent and aggressive lymphoma. It dichotomizes by aggressive disease. You should rephrase this sentence.

Reply: The controversial sentence was deleted.

181-182: Would avoid trend statements. This was not statistically significant.

Reply: It has been modified.

198: Do you mean "...when removing Watanabe...."

Reply:YES

199-200: If you are noting it is higher but not statistically significant, please add each ratio in the text.

Reply: Is it ok to have RR here?

199: "Patients" should not be capitalized

Reply: It has been modified.

213: Do you mean PFS when you say FPS?

Reply: It's a clerical error. It has been modified.

213: "...which is inconsistent with previous findings." This needs to have a reference associated to it if you are making this claim.

Reply: It has been modified.

213-216: This sentence does not make grammatical sense. Also needs to be referenced if you are going to make the claim that clinicians think RCHOP-14 is more toxic.

Reply: This sentence has been removed from the text.

219: Do you mean toxicity not toxic? Should you refer to this as a meta-analysis?

Reply: The two words mean the same thing.

226-227: This sentence should be proof-read for grammar.

Reply: It has been modified.

228: "...more likely to occur anemia events." Needs to be proof-read for grammar.

Reply: The sentence has been rewritten.

229: The heterogeneity could possibly be due to the heterogeneity of your inclusion population. You included both indolent and aggressive lymphoma in the same category and may have skewed the data. Would go back to your methods and confirm you wanted to add indolent to this category.

Reply: 229: The repetitive population was not included in the included literature. The high heterogeneity may be due to the inconsistency between B cell NHL and chemotherapy cycle. When inert indolent lymphoma is excluded from toxicity, the heterogeneity is still very high, and we believe that more RCT is needed to explore the underlying causes of heterogeneity.

Table 3: It may be easier to display Pts with SAE/total patients as a ratio (%)

Reply: It has been modified.

Table 3. Incidence and relative risk of specific severe adverse events (SAEs) in included trials

Specific adverse events	Number	RCHOP-14 Pts with SAE/total patients	RCHOP-21 Pts with AE/total patients	Relative risk (95% CI)	P value	Heterogeneity P value	Heterogeneity I^2 (%)
Neutropenia	5	53.88	63.63	0.93(0.64-1.36)	0.71	< 0.0000	98
Thrombocytopenia	5	0.07	0.09	0.87(0.60-1.25)	0.44	0.15	41
Anemia	4	0.15	0.11	1.15(0.88-1.50)	0.29	0.48	0
Febrile neutropenia	3	0.10	0.13	0.66(0.33-1.30)	0.23	0.001	85
Infection	4	0.16	0.16	1.18(0.72-1.91)	0.51	0.0003	84
Gastrointestinal toxicity	4	0.05	0.05	1.00(0.73-1.38)	0.98	0.52	0
Increase in amount of	3	0.04	0.04	1.04(0.58-1.86)	0.9	0.99	0
Cardiac-rela	3	0.02	0.02	1.04(0.15-7.34)	0.97	0.02	74
Neurological-related	3	0.08	0.05	1.41(0.85-2.33)	0.18	0.19	40