Peer Reviewer File

Article information: http://dx.doi.org/10.21037/tp-20-178.

Reviewer Comments

Thank you for the opportunity to review this manuscript. Dai et al. reported a meta-analysis of the safety and efficacy of pegylated asparaginase (PEG-asp) compared to E. coli-derived asparaginase in Chinese children with acute lymphoblastic leukemia (ALL). Consistent with reports from other populations, they observed comparable efficacy between the two, but shorter hospital stays, less frequent administration, and lower rates of certain adverse reactions in children treated with PEG-asp. The argument could be made that PEG-asp therefore reduces demands on the healthcare system and may improve patient quality of life, which is relevant to the current provisional approval this drug is prescribed under in China.

For the most part, the methodology is appropriate and clearly described. The language is adequate. I do have several suggestions for the authors, which I believe would strengthen the manuscript. I would like to see the authors respond to these points before I could recommend that the paper be published.

1. Introduction, Page 3. The authors note that the current agreement dictating the indication for PEG-Asp is only valid through the end of 2020, hence the timeliness of their work. The authors do not take an explicit position on whether they recommend the use of PEG-Asp, however. Perhaps the authors could indicate in the conclusions whether continued approval of PEG-Asp is warranted based on their findings?

Thanks for pointing out this omission in our manuscript. We added an explicit positionin the section Conclusions. The supplements were written as "Therefore, based on the conclusion of this meta-analysis, we recommend the use of PEG-Asp, and expect a period extension of PEG-Asp in the MRDL through national drug price negotiation in 2020." (see Page 16, line 13-15)

2. Introduction, Page 3. The authors state that ALL accounted for 81.8% of childhood

malignant tumors in 2018. This statistic is almost certainly incorrect. ALL probably accounts for ~82% of childhood LEUKEMIA, but more like one-third of childhood cancer. See for example this Lancet publication on the global burden of childhood cancer: https://www.thelancet.com/journals/lanonc/article/PIIS1470-2045(19)30339-0/fulltext.

"The number of ALL cases account for 81.75% in 2018 of total childhood malignant tumor in the same period, up from 34.78% in 2008." We referred to a Chinese research (Gong A, et al [2]). In this research, authors recorded 586 hospitalized children under the age of 15 with ALL who were newly diagnosed from 2008 to 2018 in Ningxia (a province of inland northwest China) to analyze the incidence and epidemiological characteristics of pediatric ALL. They also recorded the number of other pediatric malignant cancers in the same period. According to their data (see Table 1), pediatric ALL accounted for 81.75% of all malignant cancers in 2018, higher than the results of other researches, as the reviewer pointed out. We contributed the higher rate to the small record range of Gong A, et al. They only recorded hospitalized patients in one hospital in a city. Maybe these samples were not adequate to reflect the whole situation of China.

We have read the paper recommended by the reviewer but found no specific proportion of pediatric ALL accounting for pediatric malignant cancers. As we didn't find any other professional epidemiological studies on pediatric ALL, we decided to refer to data from NCCN Clinical Practice Guidelines in Oncology (2020) [1]. We modified our text as "Acute lymphoblastic leukemia (ALL), characterized by the proliferation of immature lymphoid cells in bone marrow, peripheral blood, and other organs, is the most common subtype of leukemia in children and adolescents, representing 75% to 80% of acute leukemias among children (1). It accounts for 25% of all childhood cancers, which makes it also the most common pediatric malignancy of all childhood cancers." (see page 4, line 9-12)

Table 1 Study of Gong A, et al: proportion of pediatric ALL accounting for pediatric malignant cancers

Year	Number of pediatric ALL	Number of pediatric malignant cancers	proportion of pediatric ALL accounting for pediatric malignant

			cancers
2008	16	46	34.78%
2009	18	48	37.50%
2010	20	56	35.71%
2011	22	54	40.74%
2012	35	75	46.67%
2013	46	87	52.87%
2014	60	106	56.60%
2015	74	122	60.66%
2016	86	142	60.56%
2017	97	138	70.29
2018	112	137	81.75%

The original paper was written in Chinese, we translated it into English for non-Chinses-speakers to read.

[1] National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines): pediatric acute lymphoblastic leukemia (version 2.2020). https://www.nccn.org/professionals/physician_gls/pdf/ped_all.pdf. Accessed 20 May 2020.

[2] Gong A, Di Y, Wang X, et al. Epidemiological Data Analysis of Childhood Acute Lymphoblastic Leukemia. Chinese Medical Record. 2019;20(10):59-62. Chinese.

3. Methods, Page 4. The definitions of hypersensitivity, hepatic injury, gastrointestinal symptoms and coagulation problems are not sufficient to allow replication of the study findings. The authors must specify the criteria for each of these, and should also comment on how homogeneous the contributing studies were with respect to their criteria.

As advised, we added detailed definitions of hypersensitivity, hepatic injury, gastrointestinal symptoms and coagulation problems in section Inclusion and Exclusion Criteria. (see page 7, line 6-13: "According to NCCN Guidelines and the Chinese Guideline for the Diagnosis and Management of Children with ALL (2018), the hypersensitivity reactions manifested clinically as urticaria, bronchospasm, angioedema, or anaphylaxis. Hepatic injury manifested clinically as elevation in

bilirubin, aspartate aminotransferase (AST) and alanine aminotransferase (ALT). Gastrointestinal symptoms included nausea, vomiting and abdominal pain. And coagulation abnormality is characterized by a decrease in prothrombin time (PT), fibrinogen, and increase in d-dimer and partial thromboplastin time (PTT).")

For these safety outcomes, all the contributing studies were designed referring to Chinese guidelines, and the same text was used to describe these complications. Data was reported in tabular form. Therefore, it was easy to identify that all included studies were homogeneous in terms of these outcomes.

4. Methods, Page 4. Did any studies evaluate other complications of asparaginase therapy, such as pancreatitis or hyperglycemia? Is there a reason these outcomes were not included in the present meta-analysis?

There were some studies that evaluated pancreatitis or hyperglycemia. Of the included studies, two studies (Shi L et al. 2019 and Xia L 2016) reported pancreatitis and only one study (Xia L 2016) reported hyperglycemia. We thought the number of studies reporting these two complications was too small to be representative.

5. The authors should consider including funnel plots to represent the risk of bias analysis.

We added funnel plots for CR and ORR to represent the risk of bias analysis as advised. (See page 13, line 6; see page 32, Figure 7) Because of a relatively small number of studies, funnel plots were not evaluated for AEs, frequency of administration and length of hospital stay.

6. Several of the included studies are at high risk of bias in one or more domain (random sequence generation, incomplete outcomes data, or selective reporting). Have the authors performed sensitivity analyses excluding these studies?

As advised, we added sensitivity analyses. Sensitivity analyses were undertaken with an exclusion of extreme dosage, any single study, and studies without random sequence generation. The results of sensitivity analyses were reported in section 3.5 Sensitivity analysis Results. (See page 12, line 6-19 and page 13, line 1-4.)

7. Results, Section 3.5, Page 7. This section is unclear. The authors refer to significant

Egger's test. However, it's they do not specify which data this test was performed on. It seems like this should be repeated for each endpoint/combination of studies, as the results are expected to vary based on the included studies. It's not clear what endpoint the authors are referring to with the RRs they present, and it's also not obvious to me that the results "changed clearly." Please revise this section for completeness and clarity.

As advised, we have modified our text into "The P-value of 0.031 (95% CI 0.82–1.44) was calculated by Egger's test based on the CR, which also suggested the presence of publication bias. The trim and fill approach was applied to generate an adjusted estimated pooled fixed effects risk ratio (RR) of 0.99 (95% CI 0.95–1.03), four studies were filled. Compared with the initial RR of 1.01 (95% CI 0.96-1.08), the adjusted RR changed mildly. It indicated that the original result was robust in spite of some publication bias. For ORR, the P-value was calculated as 0.125 (95% CI -0.28–2.00), indicating no presence of publication bias." But Egger's test was not evaluated for AEs, frequency of administration and length of hospital stay for a relatively small number of studies. (See page 13, line 6-15.)

8. Page 8, line 2. "…once and a total of twice" is strange phrasing. The authors mean that patients received two doses of 2500U/m^2 PEG-Asp. Also, at the end of this paragraph, the authors mention that they removed extreme doses of E. coli asparaginase. This should be stated earlier, in the Methods.

As advised, we have modified our text into "Patients in the PEG-Asp group often received a similar dosage, two doses of 2500U/m2 PEG-Asp." (See page 13, line 19 and page 14, line 1) And we added a statement in the Methods "Sensitivity analyses were undertaken with an exclusion of extreme dosage, any single study and studies without random sequence generation." (See page 9, line 3-5)

9. Page 9, line 27. The authors should revise the sentence "The results are more macroscopic, representative." This is vague and not very informative to the reader. Do the authors mean that the results are more representative of the response to asparaginase in the Chinese or East Asian population?

Yes. That's what we're trying to say. We have modified our text as advised. (See page 16, line 19, and page 17, line 1. "The results are more representative of the response to PEG-Asp and E. coli L-Asp in the Chinese population.")

10. Figure 1. There is a typo – PubMe should be PubMed.

This typo had been amended.

11. Where are the figure legends? These need to be included to describe the symbols in Figure 2, and the outcomes in Figures 3-4. Currently, it is not possible to tell which outcome is being evaluated in Figure 3 and which in Figure 4 without referring to the text.

We added figure legends for Figure 2 and captions for Figures 3-4.