

Dear Editor,

We really appreciate the critical reading of our manuscript entitled “*Hematopoiesis reconstitution and anti-tumor effectiveness of Pai-Neng-Da Capsule in acute leukemia patients with haploidentical hematopoietic stem cell transplantation*” (Manuscript No.: 70852, Retrospective Study), and we thank you for all the valuable suggestions received from the reviewers. We have carefully considered the comments and have revised the manuscript accordingly. The responses to the comments are listed one by one as follows (*please see below*).

We are looking forward to hearing about your final decision.

Kind Regards

Rui-lan Gao

Reviewer #1:

Major:

1) Since this is a retrospective study, it is not specified how allocation to treatment was chosen: please report criteria for PND administration. Moreover, it is curious that in 60 consecutive patients almost half received the treatment and half not; and that the 2 cohorts are perfectly matched; this seems much more a case-control study: please comment further.

Response: Thank you very much for your constructive suggestion. Accordingly, we have revised the “*patients and donors*” section of the MATERIALS AND METHODS.

2) the study was conducted also in children 2-year old. How was the dose of PND determined in such a population.

Response: Thank you for your comment. The following part has been added to the MATERIALS AND METHODS section: “*Pediatric patients (< 14 years old) were given PND Capsule 4 mg/kg/day (integer capsules were taken according to clinical operability). Adult patients were given two capsules at a time, three times/day.*”

3) the authors report a reduced frequency of transfusions but do not give any measure of that. Frequency of transfusions of the 2 cohorts are needed.

Response: Thank you for your comment. The frequency of transfusions is summarized in **Table 3**.

4) What grading scale of side effects was used? ctcae?

Response: Thank you for your comment. The following part has been added to the MATERIALS AND METHODS section: *According to the criteria established by the Center for Adverse Drug Reaction Monitoring of the Ministry of Health and the five-level classification, adverse drug reactions were assessed using the following levels: certain, probable, possible, suspicious, and impossible; the first four levels were judged as possibly related to the investigational drug.*

5) Several studies highlighted the role of some cytokines (tnf-alpha, ifn-gamma) in the pathogenesis of graft failure/poor graft function; please comment in the discussion section how PND may interact with them.

Response: Thank you very much for your careful review and suggestion. In the DISCUSSION section, we further discussed the relationship between PND and some cytokines (tnf-alpha, ifn-gamma) in the pathogenesis of graft failure/poor graft function.

Minor:

1) more biology on effects of PND should be reported also in the introduction.

Response: Thank you for your suggestion. We further discussed the effects of PND in the INTRODUCTION section.

2) methods: source of stem cell is lacking? Bm, pbsc, both?

Response: Thank you for your reminder. Hematopoietic stem cells were derived from both bone marrow and peripheral blood. This part has been added to the Materials and Methods section.

3) figure 1: median or mean? Add error (as sd, sem, ..) or range

Response: Thank you for your question. Data shown in **Figure 1** are means. Data on Standard Deviation are shown in **Table 2**.

4) discussion" " It was confirmed that PND Capsule could decrease the

myelosuppression caused by chemotherapy, accelerate hematopoietic function recovery, especially for erythroid and megakaryocytic lineages, following haplo-HSCT. ". Too strong for a retrospective study. Smooth the sentence.

Response: Thank you for your comment. This part has been revised.

5) part of the discussion on anti-cancer effect is too weak. Synergy with chemotherapy cannot be argued since PND was given from day +6. Expand further.

Response: Thank you for your comment and suggestion. Accordingly, this part has been revised.

Reviewer #2:

1. The authors have submitted the ethical review in attachment. This information should be showed in the Materials and Methods section.

Response: Thank you for your comment and suggestion. Accordingly, this part has been revised.

2. What is the definition of Western Medical Evaluation Standards? The authors should show it clear in the Materials and Methods section.

Response: Thank you very much for your suggestion. Accordingly, this part has been revised.

3. In this study, univariate approaches were applied to demonstrate importance of PND in acute leukemia patients. Moreover, the authors have provided much information on these patients in Table1. I would suggest that the author re-analyse their data using multifactor models (for example logistic model or cox regression model) or similar analysis. Also, could the author provide the hazard ratio of PND?

Response: Thank you for your suggestion. The limited number of cases in this study cannot meet the requirements for the number of cases in multivariate model analysis. Furthermore, no differences were observed in the baseline data between the two groups, although univariate approaches were applied to demonstrate the importance of PND in acute leukemia patients in this study.

4. In this study, conditioning regimen is CTX+Ara-C, which is not a conditioning

regimen recommended by the standard. Is the implantation effect impacted by the conditioning regimen? The PGF of the non-PND group is as high as 25.8%.

Response: Thank you for your question. The conditioning regimen in our study adopted the “Beijing Protocol”. Haplo-HSCT following “Beijing protocol” demonstrated similar efficacy to HLA-matched HSCT, which has become the predominant strategy for allogeneic HSCT in China as well as inspiration for refinement of global practice. Therefore, the conditioning regimen in this study may not be the factor affecting results.

5. Figure 1C shows platelets count over 20 on the about twelfth day after transplantation in both groups, which means most of them are implanted. Why does PGF still appear?

Response: Thank you for your question. Since data shown in Figure 1 are means, the platelet count of several patients was still $< 20 \times 10^9/L$ approx—twelfth day after transplantation in both groups.

Data on Standard Deviation are shown in **Table 2**.

6. The manuscript only mentions the incidence of aGVHD. What is the proportion of mild, moderate, and severe?

Response: Thank you for your comment. Accordingly, this part has been revised.

7. What are the common infections in the course of illness? Is there a difference in the severity of the two groups? Does it affect the prognosis? Does this affect hematopoietic reconstruction?

Response: Thank you for your careful review and help.

Recent studies have shown that CMV infection is a major risk factor for poor graft function after allo-HSCT. In our study, cytomegaloviremia and pneumonia were the main infections following allo-HSCT (within 100 days). No statistical differences were observed in infectious complications between the two groups.

The incidence of cytomegaloviremia, pneumonia, sepsis, and other infections are shown in **Table 3**.

8. In Fig.2, the author performed Kaplan-Meier survival analysis to explore the influence of PND in acute leukemia patients. In consideration of the long-term follow-up required to study the role of PND in the prognosis of acute leukemia, I

recommend the authors to retrieve the clinical demographic information of patients with a follow-up time of over 6 months, which might help to minimize the impact of prognosis due to non-PND-related reasons.

Response: Thank you for your suggestion. Only one patient in each group had a follow-up time that was shorter than 6 months. The effect may be minimal.

9. The English writing needs to be substantially improved.

Response: Thank you for your comment. A professional English proofreading company (MedSci Co., LTD) revised the manuscript.

Science editor:

This report is with great useful for understanding of hematopoiesis reconstitution and anti-tumor effectiveness of Pai-Neng-Da Capsule in acute leukemia patients with haploidentical hematopoietic stem cell transplantation.

Language Quality: Grade B (Minor language polishing)

Scientific Quality: Grade B (Very good)

Response: Thank you very much for your comment.

Company editor-in-chief:

I have reviewed the Peer-Review Report, full text of the manuscript, and the relevant ethics documents, all of which have met the basic publishing requirements of the World Journal of Clinical Cases, and the manuscript is conditionally accepted. I have sent the manuscript to the author(s) for its revision according to the Peer-Review Report, Editorial Office's comments and the Criteria for Manuscript Revision by Authors. Please provide the original figure documents. Please prepare and arrange the figures using PowerPoint to ensure that all graphs or arrows or text portions can be reprocessed by the editor. Authors are required to provide standard three-line tables, that is, only the top line, bottom line, and column line are displayed, while other table lines are hidden. The contents of each cell in the table should conform to the editing specifications, and the lines of each row or column of the table should be aligned. Do not use carriage returns or spaces to replace lines or vertical lines and do not segment cell content. Please upload the approved grant application form(s) or funding agency copy of any approval document(s).

Response: Thank you very much for your careful review and suggestion. We have

prepared figures, tables and the approved grant application forms according to your comment.