

Peer Review File

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Reviewer A

The paper titled “Chinese physician perception on the treatment of chemotherapy-induced anemia: online survey study” is interesting. This survey shows that in nearly 24% of patients undergoing chemotherapy with anemia in China, anemia may lead to interruption of chemotherapy and that the initiation of anemia treatment is not implemented in timely fashion. Most physicians prioritize Hb<80g/L as the initial Hb for chemotherapy patients with symptoms of anemia (n=149, 45%) and without symptoms of anemia (n=146, 45%). However, there are several minor issues that if addressed would significantly improve the manuscript.

1) What is the effect of chemotherapy-induced anemia on dose reduction and dose delay? Suggest adding relevant content.

Reply: we have modified our text as advised (see Page 3, line 95)

A randomized controlled trial (RCT) of non-Hodgkin’s lymphoma (NHL) patients treated with cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP), shows that those with a relative dose intensity (RDI) greater than 70 % experienced better 5-year survival compared to those receiving 70% or less ($p < 0.0009$). In a retrospective cohort study including NHL, breast, lung, gastric, ovarian, or colorectal cancer patients, they reported that moderate (grade 2) to severe (grade 3–4) anemia increased the risk of DDR in subsequent chemotherapy cycles [odds ratio (OR) = 1.46, 95 % CI (1.32, 1.62) and OR = 2.02 (1.41, 2.89)], respectively, compared to grade 1 or no anemia. Both stage I–III and IV patients with grade 2 or greater anemia were at higher risk for DDR than patients with grade 1 or no anemia [OR_{stage IV, grade 2} = 1.94 (1.58, 2.38); OR_{stage IV, grade 3/4} = 2.83 (1.42, 5.62) and OR_{stage I–III, grade 2} = 1.33 (1.18, 1.49); OR_{stage I–III, grade 3–4} = 1.81 (1.18, 2.76)]. It is essential to prompt clinical management of chemotherapy-induced anemia to avoid modifications of scheduled chemotherapy which associated with reduced treatment efficacy and poorer patient outcomes (21).

2) There are symbol errors in the results section of the manuscript. Please carefully check and make corrections.

Reply: we have modified our text as advised

3) What are the benefits and harms of iron supplementation alone and as an adjunct to ESAs compared with ESA alone in the treatment of chemotherapy-induced anemia? Suggest adding relevant content.

Reply: we have modified our text as advised (see Page 4, line 129)

In CIA patients with absolute iron deficiency, IV iron monotherapy has demonstrated efficacy and safety with no clinically significant adverse events especially with third generation compounds. In CIA patients with function ID, IV iron in combination with ESAs for CIA has the capacity to increase Hb level, improve QoL, reduce transfusion requirements and lower ESAs doses. The toxicity of IV iron included immunological effects, transfusion reactions, pains, allergic reaction, infection etc.

4) In the introduction of the manuscript, it is necessary to clearly indicate the knowledge gaps and limitations of prior study and the clinical significance of this study.

Reply: we have modified our text as advised (see Page 3, line 143)

The well-known European Anaemia Cancer Survey (ECAS) discussed the incidence, prevalence and principles of treatment of CIA as clinical practice based on patient data in 2004 (7). Song et al. published the survey conducted in 2012 provided the prevalence and treatment of cancer-related anemia data in China (6). However, most survey based on the patient data could not reveal the process of evaluation and decision-making for CIA treatment from a clinician's perspective.

The clinical significance of this study is that it is the first survey to understand CIA treatment in China from a physicians' perspective.

5) It is suggested to increase the latest progress in evaluating the relationship between anemia, fatigue, and quality of life in cancer patients, providing new insights into these closely related factors.

Reply: we have modified our text as advised (see Page 3, line 91)

A recent case-control analysis demonstrated that cancer patients with anemia showed lower QoL than non-anemic cancer patients (45.6 vs. 58, respectively; mean difference: -12.4, $p < 0.001$) and lower score in fatigue (48.0 vs. 35, respectively; mean difference: +13, $p < 0.001$) (23).

6) Will future research provide a new classification for chemotherapy induced anemia? If so, how may it be classified? Suggest adding relevant content.

Reply: The future research will not provide a new classification. The Chinese anemia grading system may modify if the blood shortage problem is solved.

Reviewer B

1) First, the title needs to indicate that this is an online cross-sectional survey.

Reply: we have modified our text as advised (see Page 1, line 4)

Chinese physician perception on the treatment of chemotherapy-induced anemia: online cross-section survey study

- 2) Second, the abstract needs some revisions. The background did not explain why Chinese physicians' perception on CIA is important and what the current knowledge gap is.

Reply: we have modified our text as advised (see Page 1, line 26)

The management of CIA remains challenging: the potential risk and benefits in providing patient-centered care need to be balanced, the disease is multifactorial, and the major treatments including RBC transfusions, ESAs and IV iron supplementation have a unique set of strengths and limitations. Also, most previous survey based on the patient data could not reveal the process of evaluation and decision-making for CIA treatment from a physician's perspective. As the comparison of CSCO, NCCN and ESMO guidelines, the standard of CIA treatment in China will vary from United States and Europe, for example, the initial Hb for RBC transfusions.

The methods need to specify the sampling method, items of the questionnaire and their response options, and how these questions were completed. The results need to briefly summarize the characteristics of the sample of Chinese physicians. The conclusion should not repeat the findings, rather please have comments on the clinical implications of the findings and the limitations of this study.

we have modified our text as advised (see Page 2, line 39)

Method: 265 samples were calculated using surveyplanet.com.

items of the questionnaire: We have answered (see Page2, line 40) impact of anemia on chemotherapy interruption, initial treatment, the target hemoglobin (Hb) level of CIA in, and the current status of erythropoiesis-stimulating agent (ESA) prescription

the question their response options, and how these questions were completed is already replied (Page 2, line 43): Respondents were asked to score their reasons for not using ESA (including safety issues, drug access in practice or adherence) and the risk options of the current treatment including ESA, red blood cell (RBC) transfusion, and iron supplementation (intravenous injection, IV).

summarize the characteristics of the sample of Chinese physicians: We have answered (see Page2, line 47)

A total of 331 questionnaires among 5,000 web visits were gathered, covering 247 hospitals in 29 provinces across China, of which 130 (53%) were tier IIIA hospitals, 50 (20%) were tier III B hospitals, 59 (24%) were tier IIA hospitals, and 8 (3%) were tier II B hospitals.

The conclusion : We have revised (see Page2, line 55)

This study is the first to conduct a large-scale survey on the diagnosis and treatment of CIA in China from a physician's perspective. We found that in China, nearly one-quarter of patients undergoing chemotherapy with concurrent anemia may

experience interruption of chemotherapy and that the initiation of anemia treatment is not adequately timed. In treating CIA, most physicians prioritize the completion of chemotherapy via Hb level over treating the symptoms of anemia.

- 3) Third, it is not inadequate to review CIA since the focus of this study is the perception of physicians on the treatment of CIA. The authors need to analyze why the perception of physicians is important and clinically needed. Please also have comments on the knowledge gap on this research focus.

Reply: we have modified our text as advised (see Page 3, line 143)

The well-known European Anaemia Cancer Survey (ECAS) discussed the incidence, prevalence and principles of treatment of CIA as clinical practice based on patient data in 2004 (7). Song et al. published the survey conducted in 2012 provided the prevalence and treatment of cancer-related anemia data in China (6). However, most survey based on the patient data could not reveal the process of evaluation and decision-making for CIA treatment from a clinician's perspective. In order to better understand the diagnosis, treatment, and unmet medical needs of patients with CIA in clinical practice, the China Medical Education Association (CMEA), in conjunction with Cancer Hope Medium, initiated the first national survey of Chinese physicians regarding the diagnosis and treatment of CIA.

- 4) Fourth, in the methodology of the main text, please describe the **clinical research design, sample size estimation, and how the question was developed and standardized**. Please explain the **theoretical basis for the development of this questionnaire**. Please also describe how the **socio-demographic variables were collected and the ethics approval of this study**. In statistics, please describe the **statistical software**. Several variables were not normally distributed. The authors need to describe the test of normality and the descriptive analysis of skewed variables.

Reply: we have modified our text as advised (see Page 5, line 160)

According to China Health Statistics Yearbook 2022 (24), there were 28.8 thousand doctors practicing in cancer hospitals in China, and based on the assumption of 95% confidence level and 5% margin of error, 265 samples were calculated using surveyplanet.com. And eventually 301 questionnaires were collected.

- 5) Finally, please cite several related papers: 1. Tartarone A, Lerosé R, Tartarone M. Erythropoiesis stimulating agents in the treatment of chemotherapy induced anemia: what do guidelines say? AME Med J 2023;8:32. 2. Greenblum G, DeLouize AM, Kowal P, Snodgrass JJ. Anemia and socioeconomic status among older adults in the Study on global AGEing and adult health (SAGE). J Public Health Emerg

2022;6:28. 3. Nastasio S, Matarazzo L, Sciveres M, Maggiore G. Giant cell hepatitis associated with autoimmune hemolytic anemia: an update. *Transl Gastroenterol Hepatol* 2021;6:25.

Reply: we have modified our text as advised (see Page 3, line 110)

We only included REF1 considering article 2& 3 is not related to chemotherapy induced anemia.