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Original Article

Clinical efficacy and toxicity of PEG-asparaginase in patients with solid tumor and ALL: a meta-analysis

Yan Lin[1,2*], Wen Liang Yu[3,4*], Pei Pei Xu[1], Quan Zhao[1], Zi Chun Hua[1,4,5]

[1]School of Life Sciences and Drum Tower Hospital Affiliated to School of Medical School, Nanjing University, Nanjing 210023, China; [2]School of Nursing, Xinxiang Medical University, Xinxiang 453000, Henan, China; [3]The State Key Laboratory of Quality Research in Chinese Medicine, Macau Institute for Applied Research in Medicine and Health, Macau University of Science and Technology, Avenida Wai Long, Taipa, Macao 999078, China; [4]Changzhou High-Tech Research Institute of Nanjing University and Jiangsu Target Pharma Laboratories Inc., Changzhou 213164, China; [5]Shenzhen Research Institute of Nanjing University, Shenzhen 518057, China. [*]Equal contributors.

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Abstract: Objective: The aim of this meta-analysis is to assess the clinical efficacy and toxicity of PEG-asparaginase in patients with solid tumor and in acute lymphoblastic leukemia (ALL). Methods: "L-asparaginase", "pegaspargase", and "PEG-asparaginase" were used as keywords to search the related articles without language limitations. "Full text", "article", "clinical research", and "completed" were used to filter the related articles and clinical data. Eleven studies containing 577 patients were enrolled in the research through the analysis of the databases of PubMed, Web of Science, Wanfang, and Clinicaltrials.gov. Results: The results indicated that completed response (CR) rate was 17% [95% confidence interval (CI): 6%-39%] and partial response (PR) rate was 2% (95% CI: 5%-11%). Patients with ALL had a better CR rate but a similar PR rate than those of patients with solid tumors. The allergic reaction rate was (95% CI: 2%-9%) and nausea vomiting rate was 13% (95% CI: 4%-34%) in all patients included in the study. More importantly, patients with ALL had a higher relapse rate but lower death rate compared to patients with solid tumors. Thus, PEG-asparaginase may be more appropriate for patients with ALL due to its low toxicity, however it still exibited challenges in clinic due to the death rate. There was publication bias in the analysis regarding CR rate, nausea vomiting rate, and death rate. Conclusion: Our findings may facilitate the understanding of the effects of PEG-asparaginase on patients with solid tumor and ALL. Our research also offered some information to the further clinical applications of the study.

Keywords: PEG-asparaginase, solid tumor, ALL, meta-analysis, subgroup analysis

Introduction

As one of the most important chemotherapy drugs, native L-asparaginase (L-ASP) has been used in chemotherapy regimens for many years [1] such as vincristine, daunorubicin, L-ASP, and prednisone (VDLP) [2]. However, in recent years, native L-ASP was replaced by PEG-asparaginase due to its serious effects in clinic [3, 4]. PEG-asparaginase is a type of covalent conjugate, which is made up of PEG and L-ASP. The main advantages of PEG-asparaginase are long acting and less allergenicity. In clinical therapy, PEG-asparaginase was used as a replacment drug of native L-ASP in patients with ALL [5]. According to the National Comprehensive Cancer Network (NCCN) guidelines, PEG-asparaginase also was the first choice in nasal NK/T-cell lymphoma (NKTL).

Although it was reckoned that PEG-asparaginase was less toxic compared to native L-ASP, especially in allergic reaction, the clinical data regarding PEG-asparaginase remained rare. The effect of PEG-asparaginase on clinical efficacy and toxicity still need more research. Thus, the study was undertaken to fill in the blanks by using meta-analysis and subgroup analysis, offering reference and suggestions to further research and rational use in clinic.

Methods

Search strategy

This was the first article where meta-analysis regarding the clinical toxicity of PEG-asparaginase was studied. Related articles were not found. Secondly, studies and clinical data

regarding the clinical toxicity of PEG-asparaginase were maken a search from the databases of PubMed, Web of Science, Wanfang, and Clinicaltrials.gov. We used "L-asparaginase", "pegaspargase", and "PEG-asparaginase" as keywords to search the related articles without language limitations. "Full text", "article", "clinical research", and "completed" were used to filter articles and clinical data. Finally, the reference lists of primary studies were reviewed by two authors. The latest search was published on October 14, 2018 [6].

Selection criteria considered for this review

All patients included in these studies suffered from ALL or solid tumor. They agreed to participate in the experimental study of the efficacy and toxicity of PEG-asparaginase. The following studies were excluded: (1) without clinical research; (2) studies unseen in clinical outcome; (3) multiple publications eliminated erroneous patient count from the same study; (4) graduation theses, editorials, abstract, and letters; (5) incomplete studies [6].

Initial review of studies

The initial database was compiled and all the duplicate articles were eliminated. We screened these citations depending on the title and abstract, which meet the inclusion criteria of the relevant studies according to the identified criteria previously [6]. After the full-text articles were assessed by two authors, final results meet the inclusion criteria performed in the review. Any problems were solved according to the ideas of two authors [6].

Data extraction

The data of initial review was recorded in a standard form of data extraction by both authors independently. The name of the first author, published year, the number of patients, patients' sex and age, drug dose, administration of two or more agents, diagnosis, clinical response, and the side effects associated with PEG-asparaginase were collected by two authors [6].

Assessment of study quality and risk of bias

Two authors (Wen Liang Yu and Yan Lin) assessed the quality of the studies (risk and bias) by the Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) tool [7]. According to the QUADAS-2 user guide [8], the items were modified for this study. In domain 1 (Patient selection), the item "Was a case-control design avoided?" was omitted. In domain 2 (Index test), the items "Were the index test results interpreted without knowledge of the results of the reference standard?" and "If a threshold was used, was it pre-specified?" were substituted with the item "Was the method for determining the outcomes of patients after administration described?". In domain 3 (Reference standard), the item "Were the reference standard results interpreted without knowledge of the results of the index test?" was omitted. In domain 4 (Flow and timing), the item "Was there an appropriate interval between index test and reference standard?" was omitted. Based on the QUADAS-2 user guide, all the research data were assessed according to the following rating scale: high risk of bias, low risk of bias, and uncertainty. Any disagreement was solved by the two authors (Wen Liang Yu and Yan Lin) [9].

Statistical analysis

Meta package (a statistical tool for meta-analysis in R software) was used to enhance the functionality of R software in meta-analysis. "Metaprop" (a special function from R software) procedures was used in this study, which allows computation of exact binomial and score test-based CI. The proportions (close to 0 or 100%) could be excluded from the meta-analysis by using it. Then, the log fit transformation was used to calculate the weighted response rate [9].

Cochran's Q test and Higgins' I^2 statistics were used to make homogeneity test for eligible studies. The data should be calculated by the random-effect model when values were considered significant heterogeneity at $P \leq 0.1$ and/or $I^2 \geq 50\%$. The data was calculated by the fixed-effect model when values were considered significant homogeneity at $P > 0.1$ and/or $I^2 < 50\%$ [9]. All the analysis was performed using Review Manager 5.3 and R software 3.5.0 [9]. The statistical analysis method based on the metaprop program of R software was used in the paper. The rate and CI value were analyzed through meta-analysis [9].

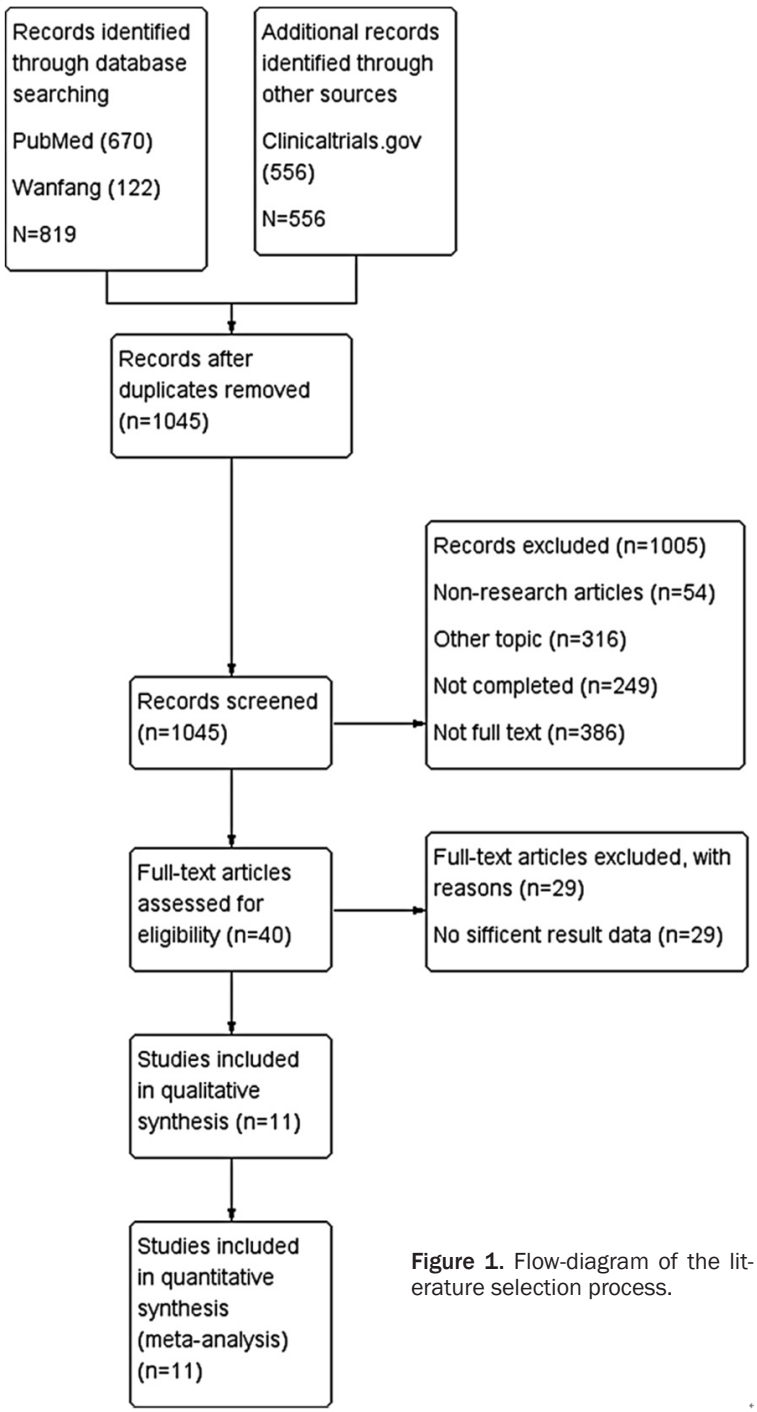

Figure 1. Flow-diagram of the literature selection process.

Results

Research results and quality assessment

The process of the literature search is shown by PRISMA flow diagram (**Figure 1**). After removing duplicates, 1045 studies from the databases of PubMed, Web of Science, Wanfang, and Clinicaltrials. gov were included in this study. Overall, 1005 studies were excluded, which included non-research-based articles (n = 54), other topic articles (n = 316), incomplete articles (n = 249), and non-full-text articles (n = 386). Furthermore, 29 studies were also excluded due to lack of detailed and credible data. Finally, 11 English articles [10-20] (**Tables 1**, **2**) were included in this research. The quality assessment of the 11 studies based on the QUADAS-2 user guidelines is shown in **Table 3**. The consistency of the selected results was higher between the two authors.

Meta-analysis of overall response rate of PEG-asparaginase in patients with solid tumors and ALL

Eleven studies [10-20] including 577 patients were enrolled in the analysis regarding overall response rate. First, overall estimate of CR rate was 17% (95% CI: 6%-39%) from the individual studies (**Figure 2**) with a significant heterogeneity (I^2 = 93%, P < 0.01). Thus, the random-effect model was used to calculate it. Then, the results indicated that CR was significantly lower in patients with solid tumors (6%, 95% CI: 1%-22%) compared to that in patients with ALL (22%, 95% CI: 8%-48%). Secondly, the overall estimate of PR rate was 2% (95% CI: 5%-11%) from the individual studies with a high heterogeneity (I^2 = 77%, P < 0.01) (**Figure 3**). Therefore, the random-effect model was used to calculate it as well. The results showed that PR of patients with ALL (2%, 95% CI: 1%-8%) was very similar compare to that in patients with solid tumor (2%, 95% CI: 0%-13%).

Meta-analysis of common side effect rate of PEG-asparaginase in patients with solid tumor and ALL patients

Eleven studies [10-20] including 148 patients were enrolled in the analysis about common

Table 1. Clinical trial characteristics

Number of patients	Sex (M/F)	Age (meant and range)	Total administration dose (IU/m^2)	Combination of drugs	Diagnosis	Responses	Ref
28	16/12	55 (26-83)	1000, 2000, 4000, 6000, 8000	No	Advanced solid cancer (malignant melanoma, NSCLC, sarcoma, colon cancer, bladder cancer1, cholangiocarcinoma, MM, renal cell carcinoma, salivary gland tumor, SCLC)	0 Died	[10]
22	10/12	60 (43-79)	250, 500, 750, 1000, 2000	No	Multiple myeloma	Median survival 31.7 months, 2 CR, 12 SD, 16 PD, 10 Died	[11]
21	16/5	1-20	8000	VCR, PED, DOX	ALL	3 Died, 3 CR, 1 PR, 2 PD	[12]
83	47/36	< 10 (61), ≥ 10 (22)	12500	Clofarabine, Ara-C, G-CSF, CTX, MTX	ALL	1 Died	[13]
32	19/13	34 (20-74)	5000	MTX, VCR, PED	ALL	30 Died	[14]
34	16/18	11.9 (1.1-16.6)	37500	VCR, PED, MTX, 6-MP, leucovorin, ARA-C	ALL	3 Died, 10 Relapses, 21 CCR, 5-year OS 76%±9%	[15]
91	48/42	46.5 (25-65)	2000	Rituximab, DNR, VCR, DXMS	ALL	36 Died	[16]
57	36/21	4.9 (1.4-15.1)	5000	No	ALL	35 Good responders, 16 Intermediate responders, 6 Poor responders	[17]
37	21/16	42 (22-69)	5000	MTX, VCR, DXMS, rituximab	ALL	140 RR, 10 CR, 3 CRp, 1 PR, 3 MLF	[18]
24	15/9	8.7	30000	Melphalan, body irradiation, CTX, BUN	ALL	10 Relapse, 5 CR	[19]
148	93/55	9.4 (0-20)	40000 or 20000	PED, DOX, VCR, HC, MTX, ARA-C	ALL	129 CR, 11 RD, 4 Died	[20]

Note: MM: multiple myeloma, SCLC: small cell lung cancer, FIB: fibrinogen, PT: Prothrombin time, PTT: prothrombin thrombin time, SD: stable disease, PD: progressive disease, AST: aspartate aminotransferase, ALT: alanine aminotransferase, LDH: actate dehydrogenase, VCR: vincristine, PED: prednisone, DOX: doxorubicin, SGOT: serum glutamic oxaloacetic transaminase, SGPT: serum glutamic pyruric transaminase, BUN: blood urea nitrogen, Ara-C: cytarabine, G-CSF: granulocyte colony stimulating factor, CTX: cyclophosphamide, 6-MP: mercaptopurine, MTX: methotrexat, DNR: Daunorubicin, DXMS: dexamethasone, HC: hydrocortisone.

Table 2. Clinical toxicity of PEG-asparaginase

Reference	Clinical toxicity
[10]	Allergic (3), amylase elevation (1), anorexia weight ↓ (3), deep vein thrombosis (2), diarrhea (5), fatigue weakness (16), FIB ↓ (2), lipase elevation (2), nausea vomiting (17), neurologic (3), PT ↑ (1), PTT ↑ (3)
[11]	Pancreatitis (3), nausea/emesis (17), abdominal pain (3), PT ↑ (14), bleeding (1), AST/ALT/LDH ↑ (13), bilirubin ↑ (4), hyperglycemia (14), hypocalcemia (13), hypoalbuminemia (4), allergic reaction (3), neocortical (2), cerebellar (3), motor (4)
[12]	Serum albumin ↑ (14), bilirubin/jaundice ↑ (14), SGOT/SGPT ↑ (14), prolonged pro time (10), prolonged PTT (24), FIB ↓ (14), nausea/vomiting (19), peripheral neuritis (5), BUN ↑ (14), fever/chills (14), pain in extremity (10)
[13]	Elevation of transaminases (39), elevation of bilirubin levels (3), elevation of transaminases (56), infectious complications (9), fever (64), stomatitis (20)
[14]	Nausea/emesis (8), diarrhea (4), mucositis (7), hyperbilirubinemia (30), hyperglycemia (26), amylase levels ↑ (7), neurologic (4), cardiac (2), coagulopathy (7)
[15]	Allergic reaction (8), pancreas (4), hemorrhage (1), thrombosis (1), transient ischemic attack (1), seizure (1)
[16]	Sepsis together with hepatotoxicity (8), neutropenic sepsis alone (3), hepatotoxicity plus bowel ischemia (2), acute coronary syndrome plus neutropenic sepsis (1), hepatotoxicity plus pancreatitis (1), pulmonary hemorrhage (1), pancreatitis (2), hepatobiliary disorders (3), allergic reaction 3, lipase ↑ (1), serum amylase ↑ (3), alkaline phosphatase ↑ (15), aspartate aminotransferase ↑ (4), blood bilirubin ↑ (17), alanine aminotransferase ↑ (10), GGT ↑ (5), triglycerides ↑ (1), hypo-albuminemia (2), Intracranial hemorrhage (1), pulmonary embolism (1), thromboembolic event (3), coagulation disorder (3)
[17]	Diabetes mellitus (1), transient hyperlipidemia (1)
[18]	AST/ALT ↑ (34), bilirubin ↑ (31), FIB ↓ (26), nausea (11), neuropathy (10), amylase/lipase ↑ (9), mucositis (8), hyperglycemia (8), diarrhea (7), thrombosis (5), vomiting (4), pleural effusion (4)
[19]	Weight ↓ (7), hypersensitivity (5), pancreatitis (2), paresthesias (1), hypoalbuminemia (12), FIB (11), functional antithrombin III (12), transaminase elevations (9)
[20]	Infection (143), low FIB (127), hypoalbuminemia (142), mucositis (141), bilirubin ↑ (143), ALT ↑ (143), weight ↓ (143)

Note: GGT: gamma glutamyl transpeptidase. ↓: decrease, ↑: increase.

side effect rate. The overall merged allergic reaction rate was 4% (95% CI: 2%-9%) from the individual studies (**Figure 4**). The heterogeneity analysis showed that it had a significant heterogeneity (I^2 = 67%, P < 0.01). Thus, the random-effect model was used to calculate it. And the results showed that the allergic reaction rate was significantly higher in patients with solid tumor (12%, 95% CI: 6%-24%) compared to that in ALL patients (2%, 95% CI: 1%-7%). The overall estimate of nausea vomiting rate was 13% (95% CI: 4%-34%) from the individual studies with a high heterogeneity (I^2 = 89%, P < 0.01) (**Figure 5**). Therefore, the random-effect model was used to calculate it. The results showed that the nausea vomiting rate was significantly higher in patients with solid tumor (68%, 95% CI: 50%-82%) compared to that in ALL patients (6%, 95% CI: 1%-23%) as well. Based on the results, patients with solid tumor may have a higher risk compared to patients with ALL in the treatment with PEG-asparaginase.

Meta-analysis of relapse rate and death rate of PEG-asparaginase in patients with solid tumor and ALL

Eleven studies [10-20] including 577 patients were included in the analysis regarding relapse rate and death rate. The overall merged relapse rate was 3% (95% CI: 1%-10%) from the individual studies (**Figure 6**) with a significant heterogeneity (I^2 = 81%, p < 0.01). Thus, the random-effect model was used to calculate it. The results showed that patients with solid tumor (2%, 95% CI: 0%-13%) had similar relapse rate compared to patients with ALL (3%, 95% CI: 1%-12%). Then, the overall estimate of death rate was 10% (95% CI: 3%-27%) from the individual studies with a high heterogeneity (I^2 = 90%, P < 0.01) (**Figure 7**). Thus, the random-effect model was used to calculate it. It indicated that death rate was higher in patients with solid tumors (13%, 95% CI: 0%-87%) than patients with ALL (9%, 95% CI: 2%-29%).

Table 3. The basic characteristics of patients in the studies included in the meta-analysis and the results of methodological quality assessment using the QUADAS-2 tool

Author, year	QUADAS					
	1	2	3	4	5	6
Taylor (2001)	Yes	Yes	Yes	Yes	Yes	Yes
Agrawal (2003)	Yes	Yes	Yes	Yes	Yes	Yes
Ettinger (1995)	Yes	Yes	Yes	Yes	No	No
Escherich (2013)	Yes	Yes	No	Unclear	Unclear	No
Aguayo (1999)	Yes	Yes	Yes	Yes	No	No
Salzer (2007)	Yes	Yes	Yes	Yes	Yes	Yes
Patel (2017)	Yes	Yes	Yes	Yes	Yes	No
Appel (2008)	Yes	Unclear	Yes	Yes	Yes	Yes
Kadia (2015)	Yes	Yes	Yes	Yes	No	No
Graham (1998)	Yes	Unclear	Yes	No	Yes	Yes
Abshire (2000)	Yes	Unclear	Yes	Yes	Yes	Yes

Note: Items of modified QUADAS-2 tool used in this study: 1. Was a consecutive or random sample of patients enrolled? 2. Did the study avoid inappropriate exclusions? 3. Was the method for determining the outcomes of patients after administration described? 4. Is the reference standard likely to classify the target condition correctly? 5. Did all patients receive the same reference standard? 6. Were all patients included in the analysis?

According to these results, patients with solid tumors had a slight lower relapse rate and higher death rate compared to patients with ALL.

Publication bias

The funnel plots were used to evaluate the publication bias for the overall estimate of all analysis regarding rate in this study (**Figure 8**). Open circles represented the studies included in the meta-analysis. The two dotted lines represented 95% CI and the two perpendicular dotted lines in the center represented the summary proportion. On the visual assessment of funnel plots, there was no evidence of publication bias to reveal the association with patients treated with PEG-asparaginase of PR rate, allergic reaction rate, and relapse rate (**Figure 8B**, **8C**, **8E**). However, the publication bias existed in CR rate, nausea vomiting rate, and death rate of patients treated with PEG-asparaginase (**Figure 8A**, **8D**, **8F**).

Discussion

As an indispensable part of various clinical chemotherapy regimens, PEG-asparaginase showed remarkable use in clinical treatment. In recent years, PEG-asparaginase played an extremely important role in partial lymphomas, such as ALL. Based on the NCCN guideline, PEG-asparaginase had been used as the first choice for patients with ALL and NKTL. However, due to its limitation of time in clinical use, some potential efficacy and safety issues are still unclear. Thus, it was necessary to make a systematic review regarding the efficacy and safety of PEG-asparaginase. This study filled in this blank by meta-analysis and subgroup analysis. Our findings may provide references for future research.

The results showed that the overall response rate of PEG-asparaginase was higher in patients with ALL compared to that in patients with solid tumor, it was also confirmed that the previous viewpoint is correct and further our method is true. Patients with ALL had a similar PR rate (2%) compared to patients with solid tumor, which indicated that the PR rate was low in patients with different tumors. According to the NCCN guideline, PEG-asparaginase was the first-line drug for patients with ALL; however, our results only confirmed that PEG-asparaginase has a better CR rate and a lower PR rate in patients with ALL. It was also undeniable that PEG-asparaginase plays an important role in patients with solid tumor, deserving further investigation and development.

These results showed that allergic reaction rate of PEG-asparaginase in all patients enrolled in the analysis was only 4% (95% CI: 2%-9%). So PEG-asparaginase can reduce allergic reaction effectively as a replacement of native L-ASP. However, the nausea vomiting rate of patients was still high, especially in patients with solid tumor. The result that patients with solid tumor had a higher common side effect rate compared to patients with ALL, further confirmed that PEG-asparaginase had not only a remarkable response rate but also a low common side effect in patients with ALL.

Our results confirmed that the relapse rate of all patients included in the analysis was very low (3%, 95% CI: 1%-10%), but death rate was

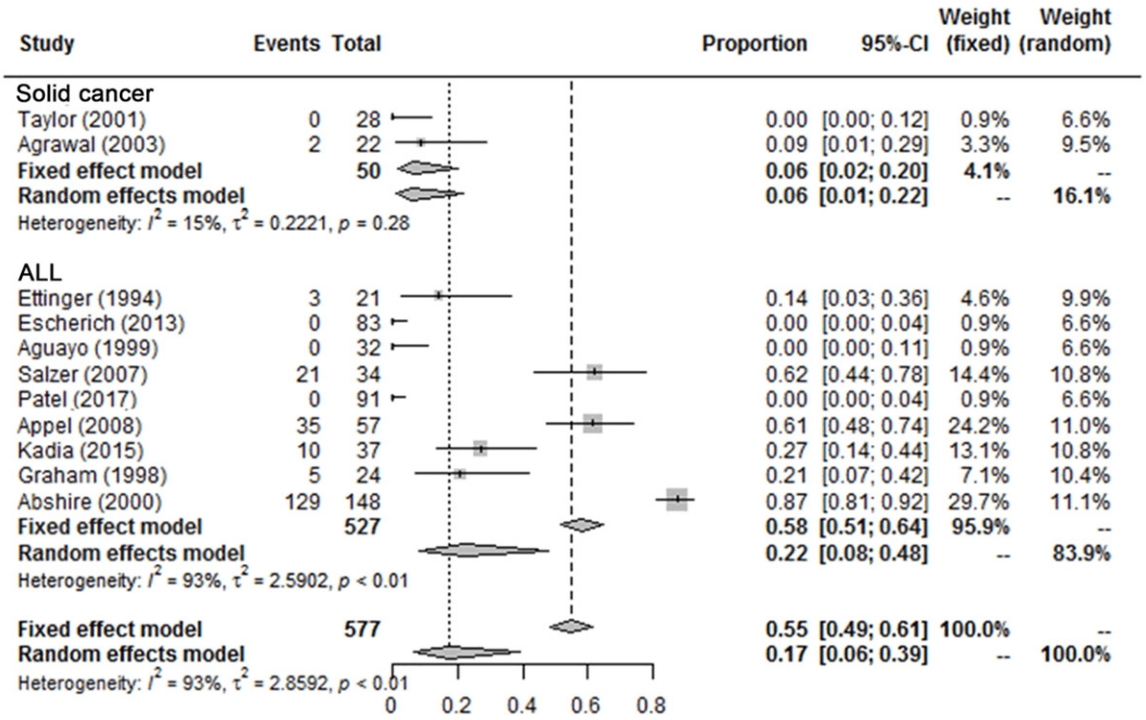

Figure 2. Forest plots of CR rate and confidence intervals in patients with solid tumor and ALL in each study and overall.

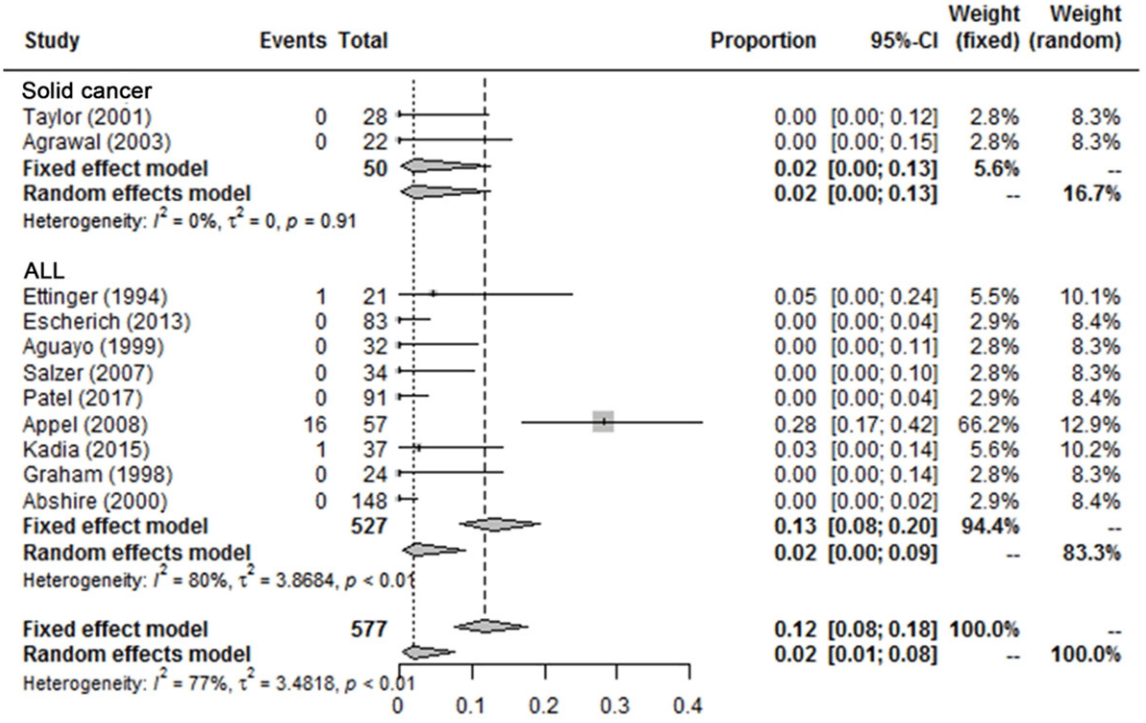

Figure 3. Forest plots of PR rate and confidence intervals in patients with solid tumor and ALL in each study and overall.

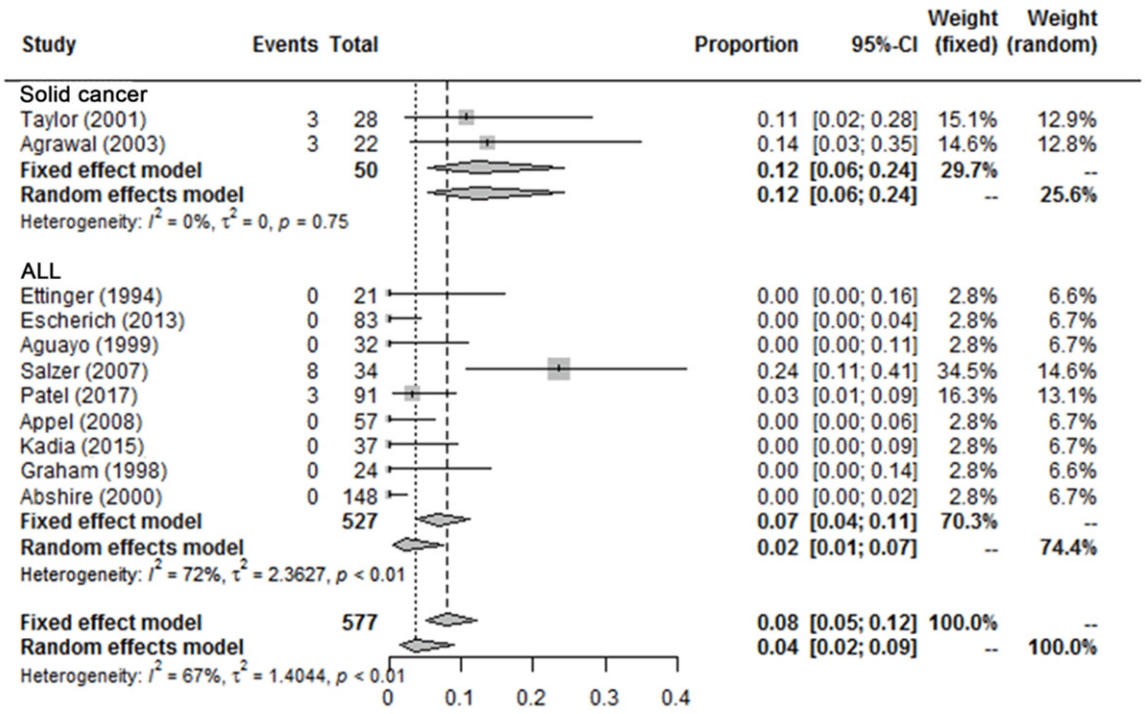

Figure 4. Forest plots of allergic reaction rate and confidence intervals in in patients with solid tumor and ALL in each study and overall.

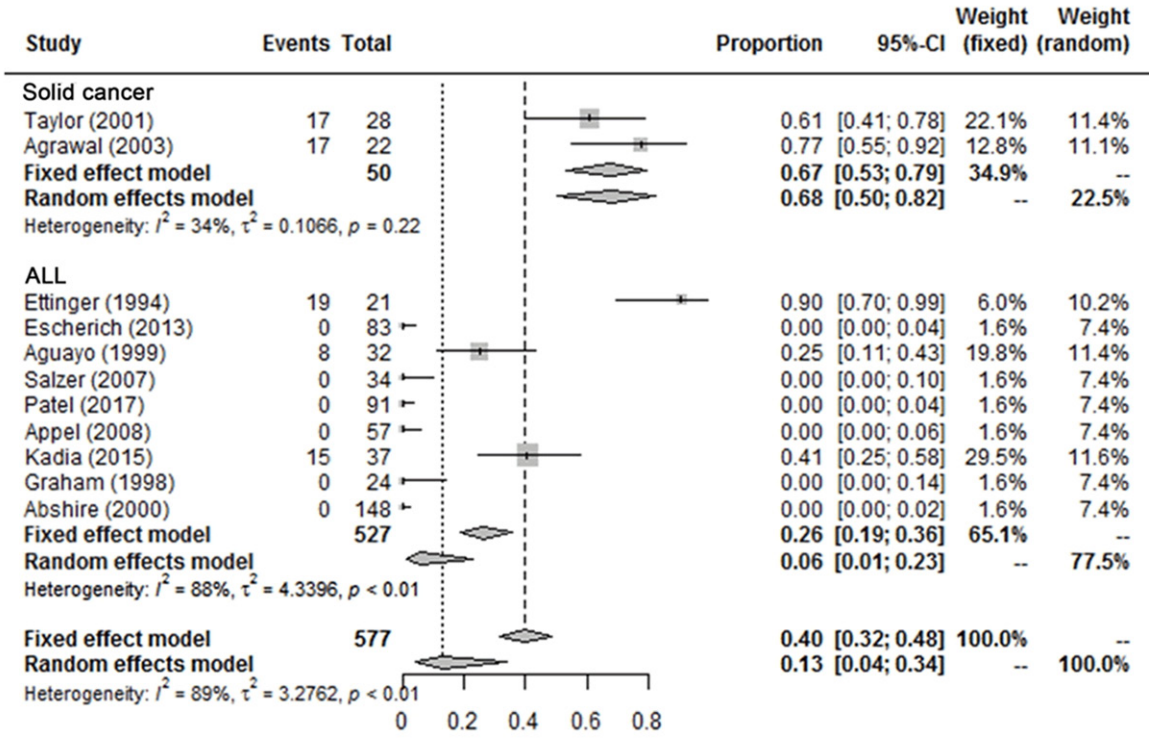

Figure 5. Forest plots of nausea vomiting rate and confidence intervals in in patients with solid tumor and ALL in each study and overall.

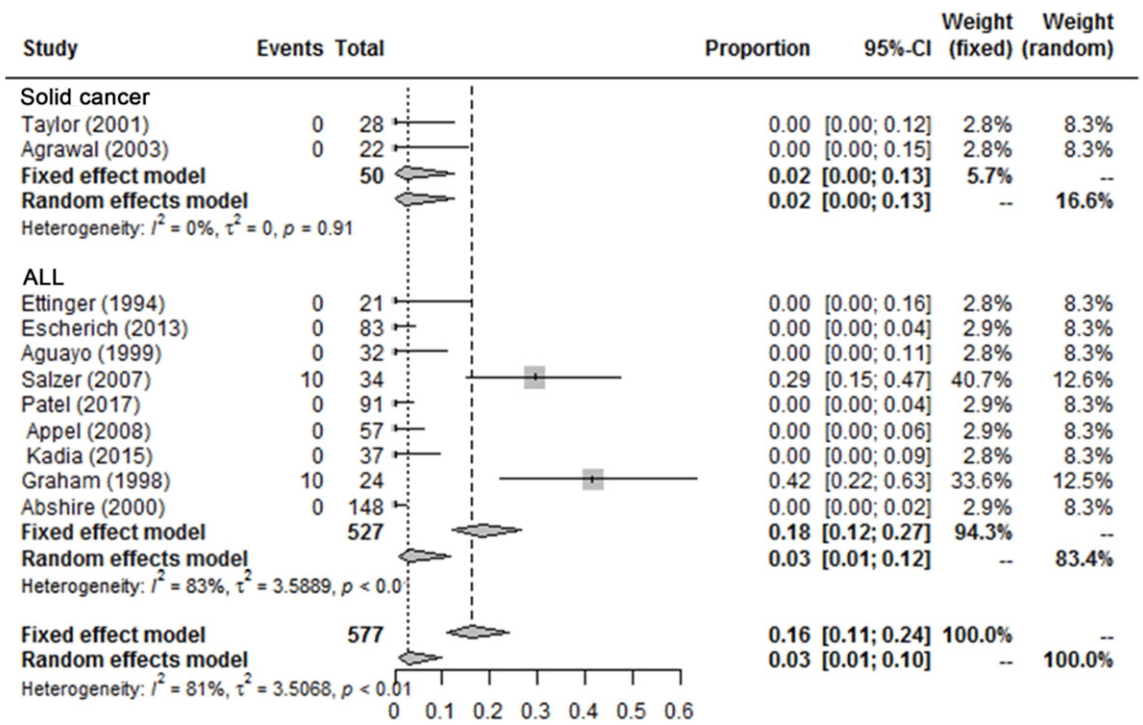

Figure 6. Forest plots of relapse rate and confidence intervals in in patients with solid tumor and ALL in each study and overall.

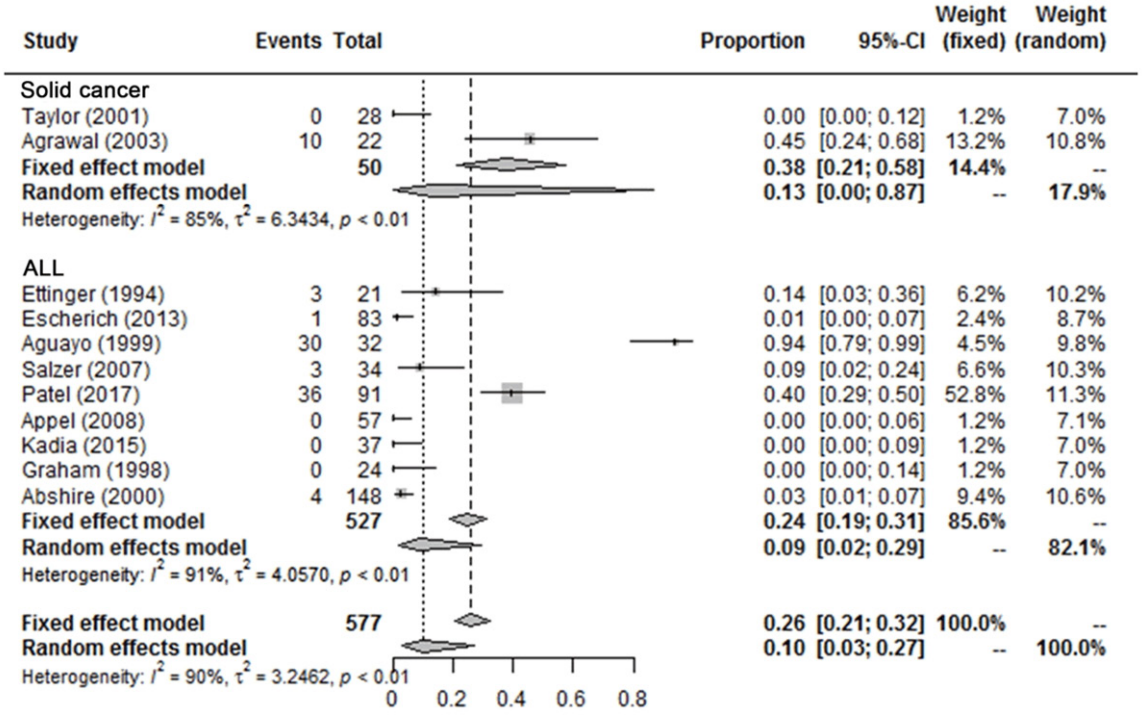

Figure 7. Forest plots of death rate and confidence intervals in in patients with solid tumor and ALL in each study and overall.

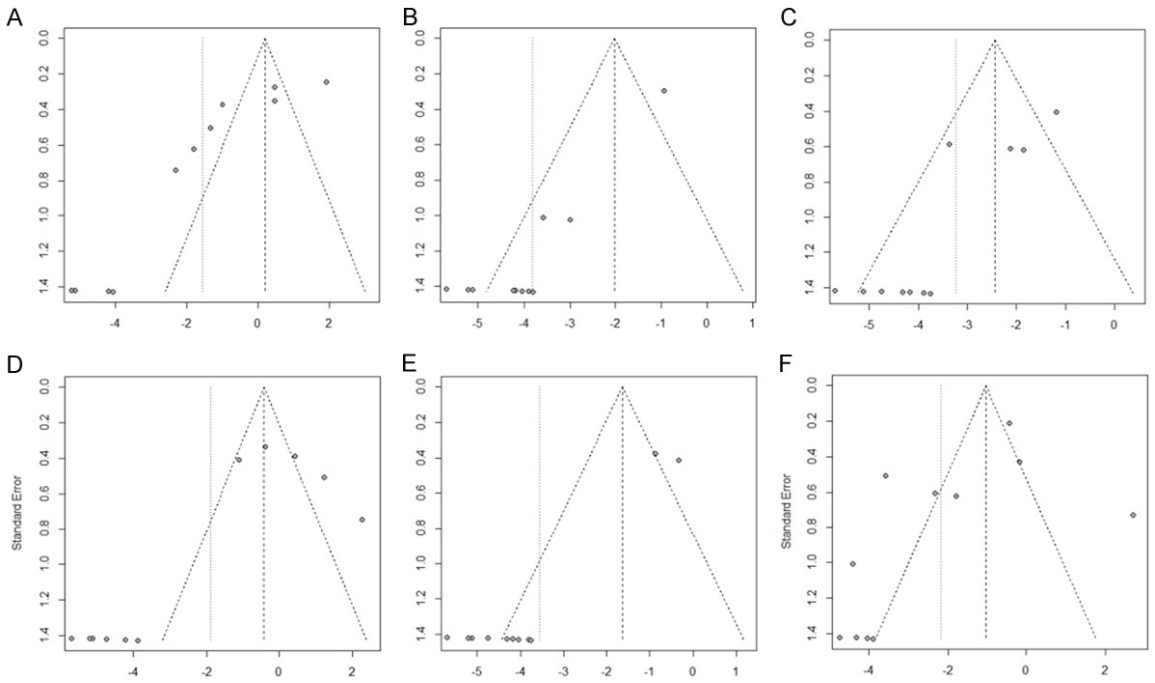

Figure 8. Funnel plots for publication bias in patients with solid tumor and ALL. A. Overall estimate of CR rate. B. Overall estimate of PR rate. C. Overall estimate of allergic reaction rate. D. Overall estimate of nausea vomiting rate. E. Overall estimate of relapse rate. F. Overall estimate of death rate. The abscissa is log fit transformed proportion, and the ordinate is standard error.

still high, even up to 13% (95% CI: 0%-87%) in patients with solid tumor. The death rate of ALL patients was 9% (95% CI: 2%-29%), which meant that PEG-asparaginase still had a serious clinical problem. Thus, although PEG-asparaginase had been widely used in clinical treatment and it achieved some obvious response, further research was still necessary. There were some potential problems in clinic, which is the reason why PEG-asparaginase was used in a systematic review.

This study also has several limitations. A first important limitation concerns different publication times, which was seen from the results of the research from 1994 to 2017. The other important limitation concerns different ages of tumor patients (from children to adult). It is believed that the errors induced by the limitations were inevitable in this study. Based on the results, the further research regarding PEG-asparaginase is necessary in the future.

The main potential heterogeneity came from "total administration dose", "whether associated with other drugs", and "the drugs of combination therapy". PEG-asparaginase is an important chemotherapy drug for chemotherapy regimens. Therefore combination therapy is inevitable. In different chemotherapy regimens, all the drugs have a different administration dose. However, the cancer types of patients are clear and the subgroup analysis can be used to make this analysis.

Conclusion

In conclusion, based on our results of this study, we found that PEG-asparaginase had a higher response rate and lower common side effect rate in patients with ALL compared to those in patients with solid tumor. More importantly, all patients included in the analysis showed a low relapse rate and a nonnegligible death rate. It was found that PEG-asparaginase was more suitable for patients with ALL compared to patients with solid tumor. However, it is necessary for further research. It also offered a reference for further clinical research and application of PEG-asparaginase. It is believed that PEG-asparaginase can continue to play an important role in cancer therapy.

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Disclosure of conflict of interest

None.

Address correspondence to: Zi-Chun Hua, School of Life Sciences and Drum Tower Hospital Affiliated to School of Medical School, Nanjing University, Nanjing 210023, China; Changzhou High-Tech Research Institute of Nanjing University and Jiangsu TargetPharma Laboratories Inc., Changzhou 213164, China; Shenzhen Research Institute of Nanjing University, Shenzhen 518057, China. Tel: 86-25-89683692; Fax: 86-025-83324605; E-mail: zchua@nju.edu.cn

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