A meta-analysis of safety and efficacy on first-line S-1 therapy in cancer patients

Yingying Miao, Ping Zhan, Tangfeng Lv, Yong Song

Department of Respiratory Medicine, Jinling Hospital, Nanjing University School of Medical, Nanjing 210002, China

Correspondence to: Tangfeng Lv. Department of Respiratory Medicine, Jinling Hospital, Nanjing University School of Medical, 305 East Zhongshan Road, Nanjing 210002, China. Email: bairoushui@163.com; Yong Song. Department of Respiratory Medicine, Jinling Hospital, Nanjing University School of Medical, 305 East Zhongshan Road, Nanjing 210002, China. Email: yong_song6310@yahoo.com.

Background: The incidence of grade 3/4 adverse effects due to S-1 therapy and the efficacy of S-1-based therapy *vs*. S-1 monotherapy have not been well described. We conducted an updated meta-analysis to evaluate this problem.

Methods: We searched the electronic databases, including PubMed, Embase, and Cochrane database to investigate the effects of phase 2 and 3 prospective clinical trials on first-line S-1 therapy in cancer patients. Data from included studies were pooled using Stata version 12.0.

Results: Twenty eight studies were included. First-line S-1 monotherapy showed low incidence of grade 3/4 adverse effects. And the highest rate grade 3/4 hematological event was neutropenia [7%, 95% confidence interval (CI): 5-8%]; the highest rate grade 3/4 non-hematological event was anorexia (7%, 95% CI: 6-9%). Longer overall survival (OS) time and progression-free survival (PFS) time was exhibited in S-1-based therapy, compared with S-1 monotherapy [hazard ratio (HR) 0.836, 95% CI: 0.761-0.911, P=0.000, and HR 0.650, 95% CI: 0.540-0.759, P=0.000, respectively]. However, the incidence of grade 3/4 adverse effects was also higher in S-1-based therapy than S-1 monotherapy in cancer patients, with relative risk (RR) of neutropenia and anorexia were respectively 4.62 (95% CI: 2.92-7.30) and 1.46 (95% CI: 0.84-2.55).

Conclusions: S-1 monotherapy was demonstrated with low incidence of high grade adverse effects, therefore it is well tolerated for majority cancer patients; S-1-based therapy significantly improved OS and PFS compared with S-1 monotherapy, with an increased risk of high grade adverse effects.

Keywords: S-1; prognosis; adverse effects; cancer; meta-analysis

Submitted Jul 21, 2015. Accepted for publication Jul 23, 2015.

doi: 10.3978/j.issn.2218-6751.2015.07.21

View this article at: http://dx.doi.org/10.3978/j.issn.2218-6751.2015.07.21

Introduction

S-1 is an oral fluoropyrimidine anticancer drug, combined with tegafur (prodrug of fluorouracil), gimeracil (dihydropyrimidine dehydrogenase inhibitor), and oteracil in a molar ratio of 1:0.4:1. It has been demonstrated to be beneficial in the treatment of many types of metastatic cancers, including advanced gastric cancer (AGC), pancreatic cancer, non-small cell lung cancer (NSCLC), colorectal cancer, biliary tract cancer, head and neck cancer and so on (1-5). Recent studies also showed that S-1 can reduce the gastrointestinal (GI) toxic effects of fluorouracil. Since the 1990s, S-1 has been used for the treatment of many types of cancers. The SAMIT, a phase 3 factorial randomized controlled trial (RCT), indicated that patients with T4a or T4b gastric cancer who were treated with S-1 therapy were superior to tegafur and uracil (UFT), therefore for locally AGC S-1 monotherapy should remain the standard treatment in Japan (6). When treated as a single agent, this drug, with high overall and relapse-free survival rates at 3 years and low incidence of adverse effects, was feasible for postoperative lung cancer patients (5).

Previous meta-analyses, which were conducted to investigate the prognostic significance of S-1-based therapy

vs. S-1 monotherapy in patients with AGC, have showed that there were significantly longer median overall survival (OS) time and median progression-free survival (PFS) time in AGC patients receiving S-1-based therapy, on the other hand, the incidence of grade 3/4 neutropenia was higher in S-1-based therapy (7). However, in that meta-analysis, the sample size was relatively small and they only compared S-1-based therapy *vs*. S-1 monotherapy in AGC patients, and we believe that those findings should be confirmed with larger studies and other tumor types. To evaluate the incidence of high grade adverse effects and the efficacy of S-1-based therapy *vs*. S-1 monotherapy in cancer patients, we conducted an updated systematic review and meta-analysis with the aim of investigating whether S-1 monotherapy is low toxic and S-1-based therapy is more effective than S-1 monotherapy in cancer patients.

Material and methods

Search strategy

We searched the electronic databases, including PubMed, Embase, and Cochrane database. The upper date limit was March 2015, with no lower date limit. Searches include the terms: ("S-1") and ("cancer", OR "carcinoma") and ("clinical trial", OR "randomized controlled trial"). The reference lists of included studies were also searched.

Eligibility criteria

The eligibility criteria for this meta-analysis are: (I) prospective phase 2 and 3 clinical trials in cancer patients; (II) the language restricted to English; (III) presented the main adverse events data of S-1 therapy; (IV) participants assigned to first-line treatment with single agent S-1 at 80-120 mg/day twice daily (the daily dose was assigned according to body surface area as follows: <1.25 m^2, 80 mg daily; ≥1.25-<1.5 m^2, 100 mg daily; and ≥1.5 m^2, 120 mg daily) on 4 weeks of a 6-week circle or 2 weeks of a 3-week circle; (V) if the same study was published in several publications, we only included the most recent, or complete. Phase I studies were excluded because of the different drug dosage and the relatively small number of patients on these trials. Two reviewers independently assess each study for inclusion.

Data extraction and quality assessment

Two reviewers independently extracted information from included studies using a traditionalized format, and a third reviewer verified them. Information collected included: first author, publishing year, trial phase, research type, tumor type, treatment arm, sample size, dosage of S-1, and the number of adverse effects (*Table 1*). And for studies with S-1-based therapy, we also collected the median OS and PFS, and the hazard ratio (HR) of PFS or OS and its 95% confidence interval (CI).

Two independent researchers conducted quality assessment of included studies using the Newcastle-Ottawa Quality Assessment Scale for case control studies and for cohort studies (30). All of the studies included had a high quality with more than five stars each one.

Data analysis

For each study, we calculated the proportion and 95% CI of the majority grade 3/4 adverse effects in cancer patients treated with S-1 monotherapy or S-1-based therapy. For studies with S-1-based treatment in the same trial, we also calculated and compared the relative risk (RR) of grade 3/4 adverse effects and the HR and its 95% CI of median OS and PFS [two (12,22) of them was derived via the methods developed by Parmar *et al*. (31)]. Heterogeneity for studies was calculated using the χ^2-based Q statistic. If $P<0.05$ or $I^2>50\%$, we could consider that there was statistically significant heterogeneity. Then data were analyzed using a random effects model. The publication bias was performed using the Begg's and Egger's tests (32,33). All of the data from included studies were pooled using Stata version 12.0.

Results

Study selection and characteristics

A total of 769 references were yielded from initial searches of the electronic database. Then 699 titles and abstracts were filtered out based on the inclusion criteria. Another 42 articles were excluded after a full-text review. Finally, we included 28 studies (19 phase 2 and 9 phase 3) comprising 2,359 participants. The flow chart of this meta-analysis is described in *Figure 1*.

Incidence of high-grade adverse events

All of the 28 studies provided grade 3/4 adverse events (*Table 2*). The total number of patients included was 2,359. No data for neutropenia and fatigue were available

Table 1 Main characteristics of the studies included in this meta-analysis

Study	Year	Phase	Research	Tumor type	Treatment arm	No. of patients	Age, years
Tsuburaya *et al*. (6)	2014	3	RCT	Gastric cancer	S-1 80-120 mg twice daily, 2-week administration/1-week rest	363	20-80
Lu *et al*. (8)	2014	2	RCT	Gastric cancer	S-1 80-120 mg twice daily, 2-week administration/1-week rest	47	18-75
Koizumi *et al*. (9)	2014	3	RCT	Gastric cancer	S-1 80-120 mg twice daily, 4-week administration/2-week rest	313	20-80
Imamura *et al*. (10)	2014	2	Single arm	Gastric cancer	S-1 80-120 mg twice daily, 4-week administration/2-week rest	35	>75
Komatsu *et al*. (11)	2011	2	RCT	Gastric cancer	S-1 80-120 mg twice daily, 4-week administration/2-week rest	47	20-80
Narahara *et al*. (12)	2011	3	Parallel arm	Gastric cancer	S-1 80-120 mg twice daily, 4-week administration/2-week rest	160	20-75
Chen *et al*. (13)	2011	2	Single arm	Gastric cancer	S-1 80-120 mg twice daily, 4-week administration/2-week rest	34	37-84
Koizumi *et al*. (14)	2010	2	Single arm	Gastric cancer	S-1 80-120 mg twice daily, 4-week administration/2-week rest	33	>75
Boku *et al*. (15)	2009	3	RCT	Gastric cancer	S-1 80-120 mg twice daily, 4-week administration/2-week rest	234	20-75
Kodera *et al*. (16)	2009	2	Single arm	Gastric cancer	S-1 80-120 mg twice daily, 4-week administration/2-week rest	46	39-79
Lee *et al*. (17)	2008	2	RCT	Gastric cancer	S-1 80-120 mg twice daily, 4-week administration/2-week rest	42	65-82
Koizumi *et al*. (18)	2008	3	RCT	Gastric cancer	S-1 80-120 mg twice daily, 4-week administration/2-week rest	150	28-74
Sakuramoto *et al*. (1)	2007	3	RCT	Gastric cancer	S-1 80-120 mg twice daily, 4-week administration/2-week rest	517	27-80
Koizumi *et al*. (19)	2000	2	Single arm	Gastric cancer	S-1 80-120 mg twice daily, 4-week administration/2-week rest	50	20-75
Tsukahara *et al*. (2)	2015	3	RCT	Head and neck cancer	S-1 80-120 mg twice daily, 2-week administration/1-week rest	251	20-75
Harada *et al*. (20)	2008	2	Single arm	Oral squamous cell carcinoma	S-1 80-120 mg twice daily, 4-week administration/2-week rest	41	20-80
Morizane *et al*. (3)	2013	2	Parallel arm	Biliary tract cancer	S-1 80-120 mg twice daily, 4-week administration/2-week rest	50	20-79
Furuse *et al*. (21)	2008	2	Single arm	Biliary tract cancer	S-1 80-120 mg twice daily, 4-week administration/2-week rest	40	20-74
Ueno *et al*. (22)	2013	3	Parallel arm	Pancreatic cancer	S-1 80-120 mg twice daily, 4-week administration/2-week rest	272	20-80
Okusaka *et al*. (23)	2008	2	Single arm	Pancreatic cancer	S-1 80-120 mg twice daily, 4-week administration/2-week rest	40	20-74
Uehara *et al*. (24)	2013	2	Single arm	Colorectal cancer	S-1 80-120 mg twice daily, 4-week administration/2-week rest	60	20-80
Mochizuki *et al*. (4)	2012	3	RCT	Colorectal cancer	S-1 80-120 mg twice daily, 4-week administration/2-week rest	756	20-80
Shirao *et al*. (25)	2004	2	Single arm	Colorectal cancer	S-1 80-120 mg twice daily, 4-week administration/2-week rest	38	20-75
Ohtsu *et al*. (26)	2000	2	Single arm	Colorectal cancer	S-1 80-120 mg twice daily, 4-week administration/2-week rest	62	27-74
Shiroyama *et al*. (27)	2012	2	Single arm	NSCLC	S-1 80-120 mg twice daily, 4-week administration/2-week rest	23	>75
Tsuchiya *et al*. (5)	2012	2	Single arm	NSCLC	S-1 80-120 mg twice daily, 4-week administration/2-week rest	50	20-80
Nishiyama *et al*. (28)	2011	2	Single arm	NSCLC	S-1 80-120 mg twice daily, 4-week administration/2-week rest	29	>70
Kawahara *et al*. (29)	2001	2	Single arm	NSCLC	S-1 80-120 mg twice daily, 4-week administration/2-week rest	59	20-75

Summary table of studies included in the meta-analysis. RCT, randomized controlled trial; NSCLC, non-small cell lung cancer.

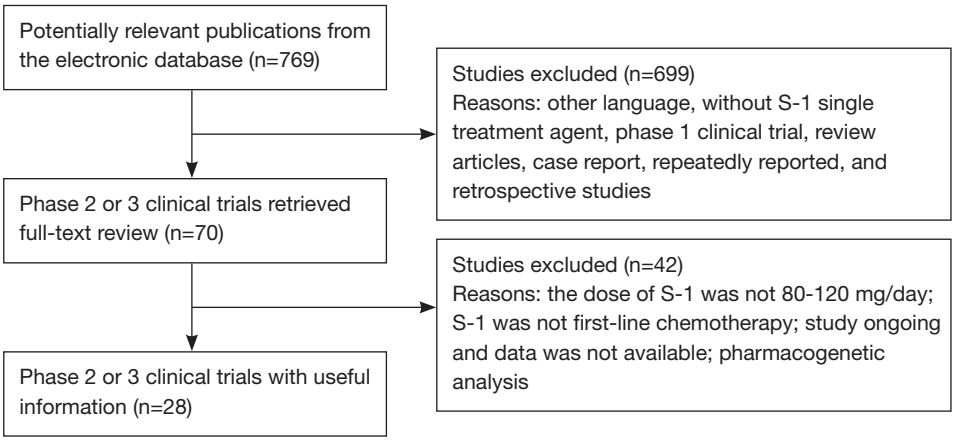


Figure 1 Selection process for the studies included in this meta-analysis.

Table 2 Outcome of grade 3/4 adverse effects summarized in S-1 monotherapy as first-line treatment in cancer patients

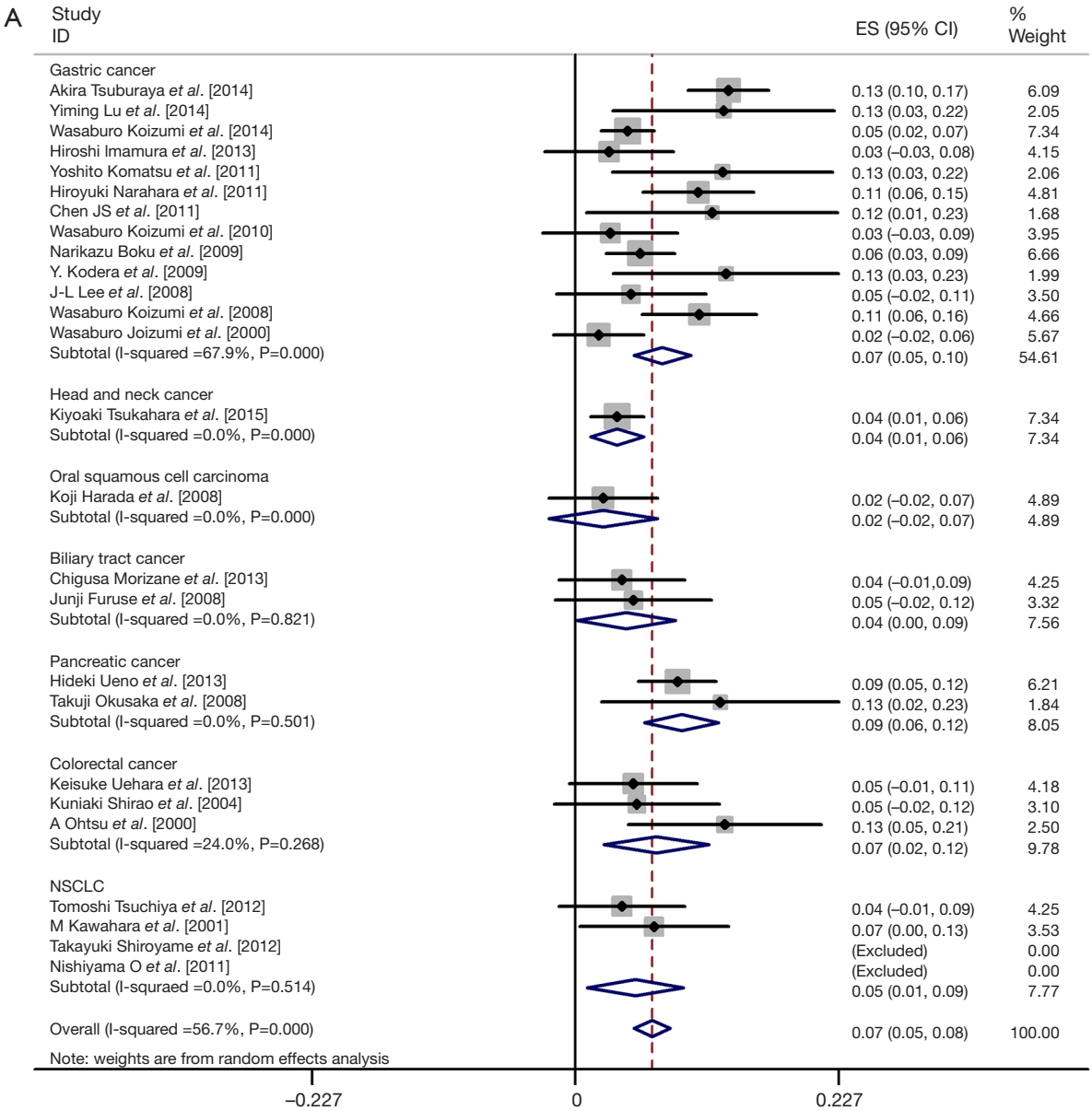
Adverse events	No. of evaluable studies	Heterogeneity		S-1 monotherapy (95% CI)
		P value	I^2 (%)	
Hematological				
Leucopenia	28	0.039	40.5	0.02 (0.01-0.03)
Neutropenia	26	0.000	56.7	0.07 (0.05-0.08)
Anemia	28	0.000	77.9	0.05 (0.04-0.06)
Thrombocytopenia	27	0.010	49.1	0.01 (0.00-0.01)
Non-hematological				
Anorexia	28	0.000	71.8	0.07 (0.06-0.09)
Fatigue	26	0.000	68.2	0.04 (0.03-0.05)
Nausea	28	0.242	16.4	0.03 (0.02-0.03)
Diarrhea	27	0.012	45.0	0.03 (0.02-0.04)

CI, confidence interval

in two studies [(1,4); (5,27) respectively]; no data for thrombocytopenia and diarrhea were available in one study [(15); (22) respectively]. Pooled data from these studies demonstrated a grade 3/4 adverse events rate of 32% for S-1 monotherapy. In addition, the grade 3/4 hematological event rate was 15% and the grade 3/4 non-hematological event rate was 17% for S-1 monotherapy as first-line treatment. The results of the meta-analysis for neutropenia and anorexia were shown in *Figure 2*. The incidence of grade 3/4 neutropenia ranged from 0 to 13%; the highest incidence was noted in a phase 3 RCT with gastric cancer (6), and the lowest incidence was observed in patients with NSCLC (27,28). However, the incidence of grade 3/4 anorexia ranged from 0 to 19%; the highest incidence was noted in a randomized phase 3 study with gastric cancer (12), and the lowest incidence was observed in patients with gastric cancer and colorectal cancer (19,25). This meta-analysis exhibited a significant heterogeneity among included studies (I^2=56.7%, P=0.00 for neutropenia and I^2=71.8%, P=0.00 for anorexia), and the calculated summary incidence of grade 3/4 neutropenia and anorexia among patients receiving S-1 was respectively 7% (95% CI: 5-8%) and 7% (95% CI: 6-9%) using a random effects model (*Figure 2*).

Subgroup analysis according to tumor type

To reduce the influence of significant heterogeneity, we carried out a subgroup analysis to confirm whether the tumor type had an influence on the incidence of high-grade adverse events with S-1 monotherapy. There was



no significant difference of occurrence of grade 3/4 neutropenia and anorexia between gastric cancer, colorectal cancer and NSCLC; in pancreatic cancer, they were a little bit higher (*Figure 2*).

Difference between S-1-based therapy and S-1 monotherapy

We also performed meta-analysis to derive a more accurate estimate of the prognostic value of S-1 based therapy *vs.* S-1 monotherapy in tumor patients (*Figures 3*,*4*). We found that the tumor patients who receiving S-1 based therapy had longer median OS time and median PFS time than those who receiving S-1 monotherapy (HR 0.836, 95% CI: 0.761-0.911, P=0.000, and HR 0.650, 95% CI: 0.540-0.759, P=0.000) (*Figure 3*). On the other hand, the RR of neutropenia and anorexia were respectively 4.62 (95% CI: 2.92-7.30) and 1.46 (95% CI: 0.84-2.55) (*Figure 4*). The incidence of grade 3/4 neutropenia was higher in patients with S-1-basedtherapy than those in S-1 monotherapy.

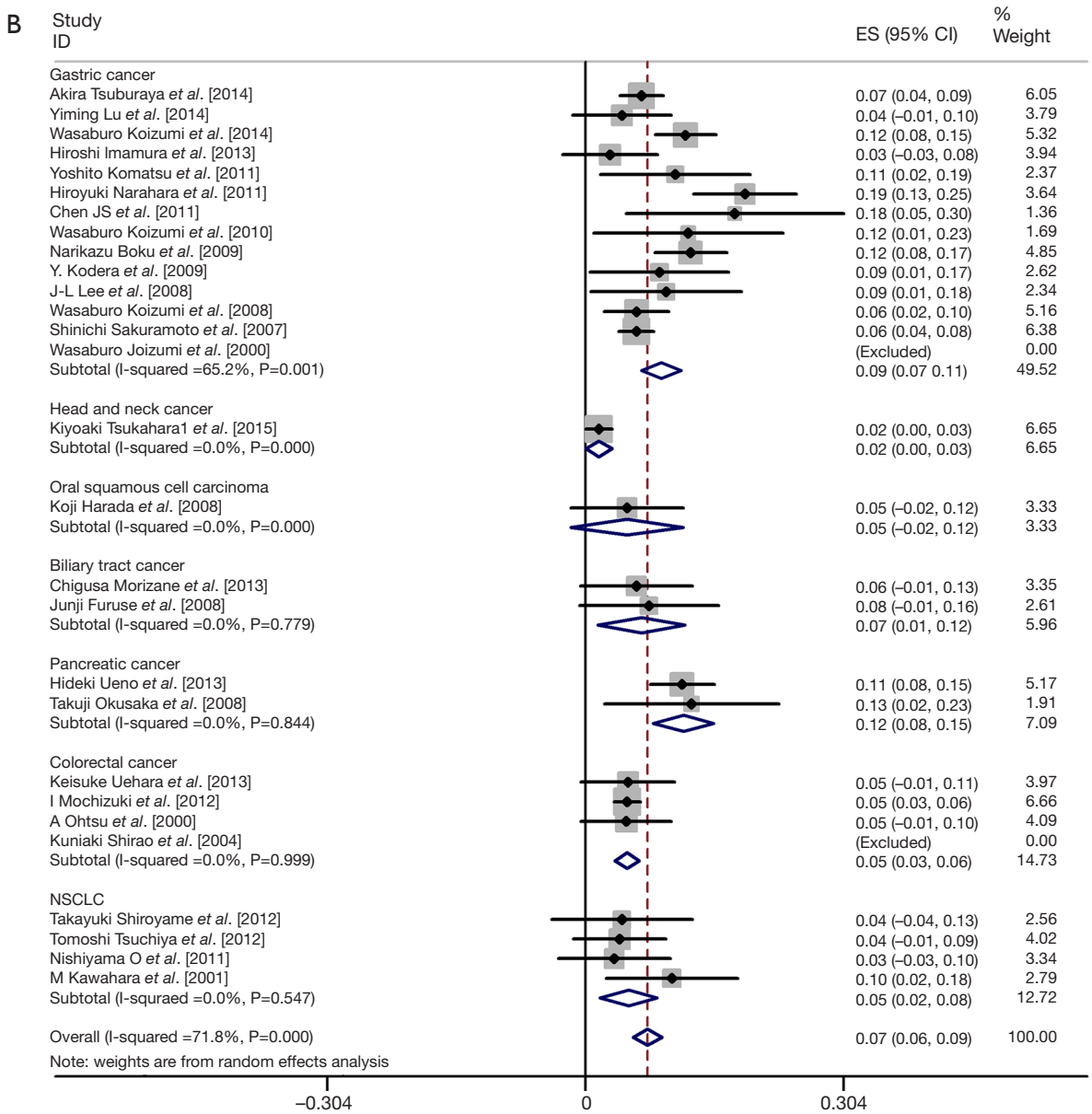


Figure 2 Forest plot for meta-analysis of incidence relative risk of high grade neutropenia and anorexia in cancer patients treated with S-1 monotherapy. Each study was shown by the name of the first author and year of publication. The subgroup analysis of tumor types and summary incidence were also shown in the figure. Plots are arranged as follows: (A) incidence of grade 3/4 neutropenia; (B) incidence of grade 3/4 anorexia. ES, effect size; CI, confidence interval; NSCLC, non-small cell lung cancer.

Publication bias

We performed Begg's funnel plot and Egger's test to evaluate the publication bias of the eligible studies. No publication bias was detected by either the funnel plot or Egger's test of grade 3/4 proteinuria neutropenia (P=0.913 and P=0.418) and anorexia (P=0.300 and P=0.840) (*Figure 5*).

Discussion

Since the 1990s, S-1 has been used for the treatment of many types of cancers. Recently a meta-analysis compared S-1 with 5-Fu (34). 5-Fu has been a main anticancer agent for malignancies since it was introduced in 1957 (35). Their meta-analysis demonstrated that there were statistically

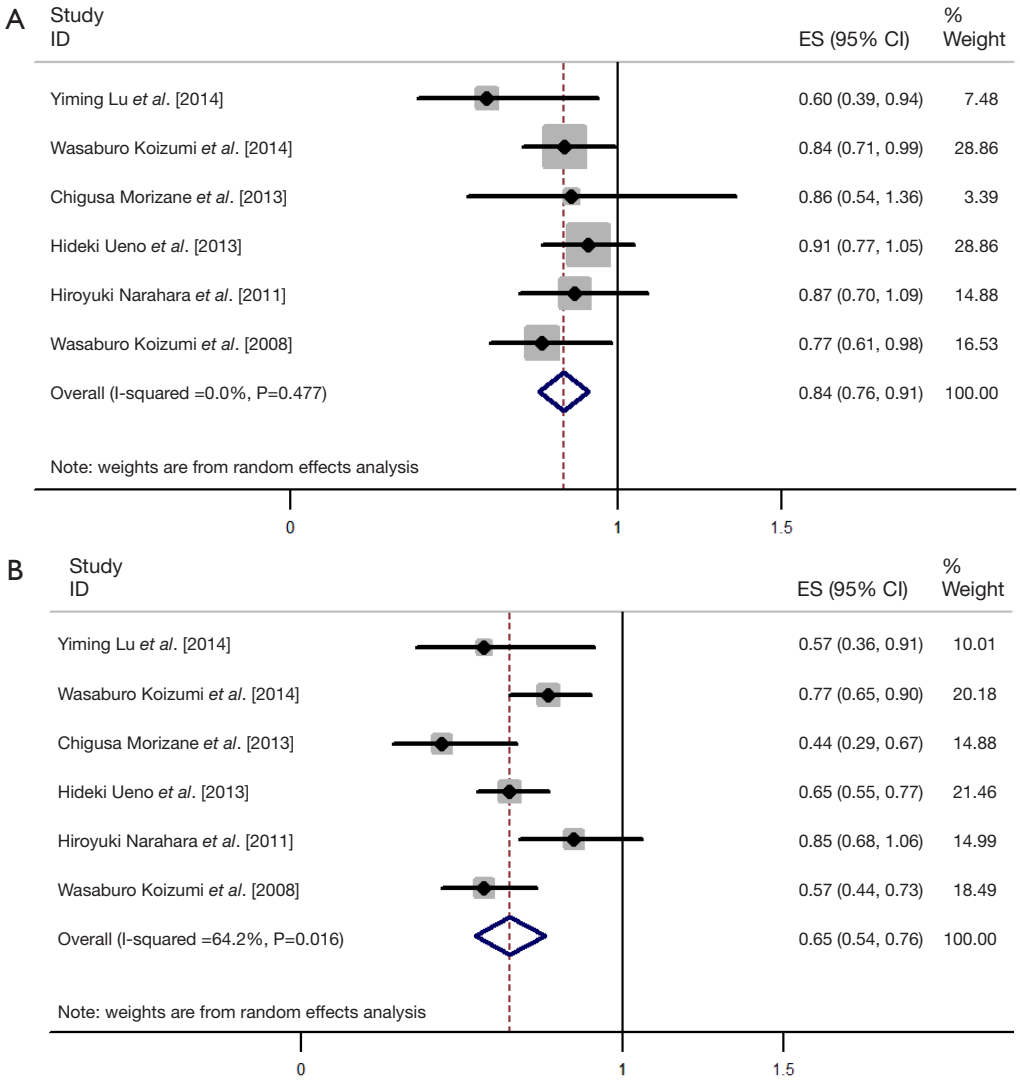


Figure 3 Forest plot for meta-analysis of overall survival (A) and progression-free survival (B) associated with S-1-based therapy compared with S-1 monotherapy in cancer patients. ES, effect size; CI, confidence interval.

significant improvements of PFS and ORR in the S-1-based chemotherapy in patients with AGC (P<0.001; P=0.005). S-1 has remarkable survival benefits, and S-1-based chemotherapy could replace 5-Fu-based therapy in advanced GI cancer in Asian patients (34).

The aim of this study is to evaluate the incidence of grade 3/4 adverse effects due to S-1 therapy and the efficacy of S-1-based therapy *vs*. S-1 monotherapy. We conducted this updated systematic review and meta-analysis to investigate whether S-1 monotherapy is low toxic and S-1-based therapy is more effective than S-1 monotherapy in cancer patients. The meta-analysis included 28 studies, including 19 phase 2 trials and 9 phase 3 trials. Our results showed that first-line S-1 monotherapy had low incidence of grade 3/4 adverse effects. The highest rate grade 3/4 hematological event was neutropenia (7%, 95% CI: 5-8%); the highest rate grade 3/4 non-hematological event was anorexia (7%, 95% CI: 6-9%). In addition, there was no significant difference of occurrence of grade 3/4 neutropenia and anorexia between gastric cancer, colorectal cancer and NSCLC; in pancreatic cancer, they were a bit higher.

We also investigated the efficacy of S-1-based therapy *vs*. S-1 monotherapy. The results of our meta-analysis showed that longer OS time and PFS time was exhibited in S-1-based therapy, compared with S-1 monotherapy (HR 0.836,

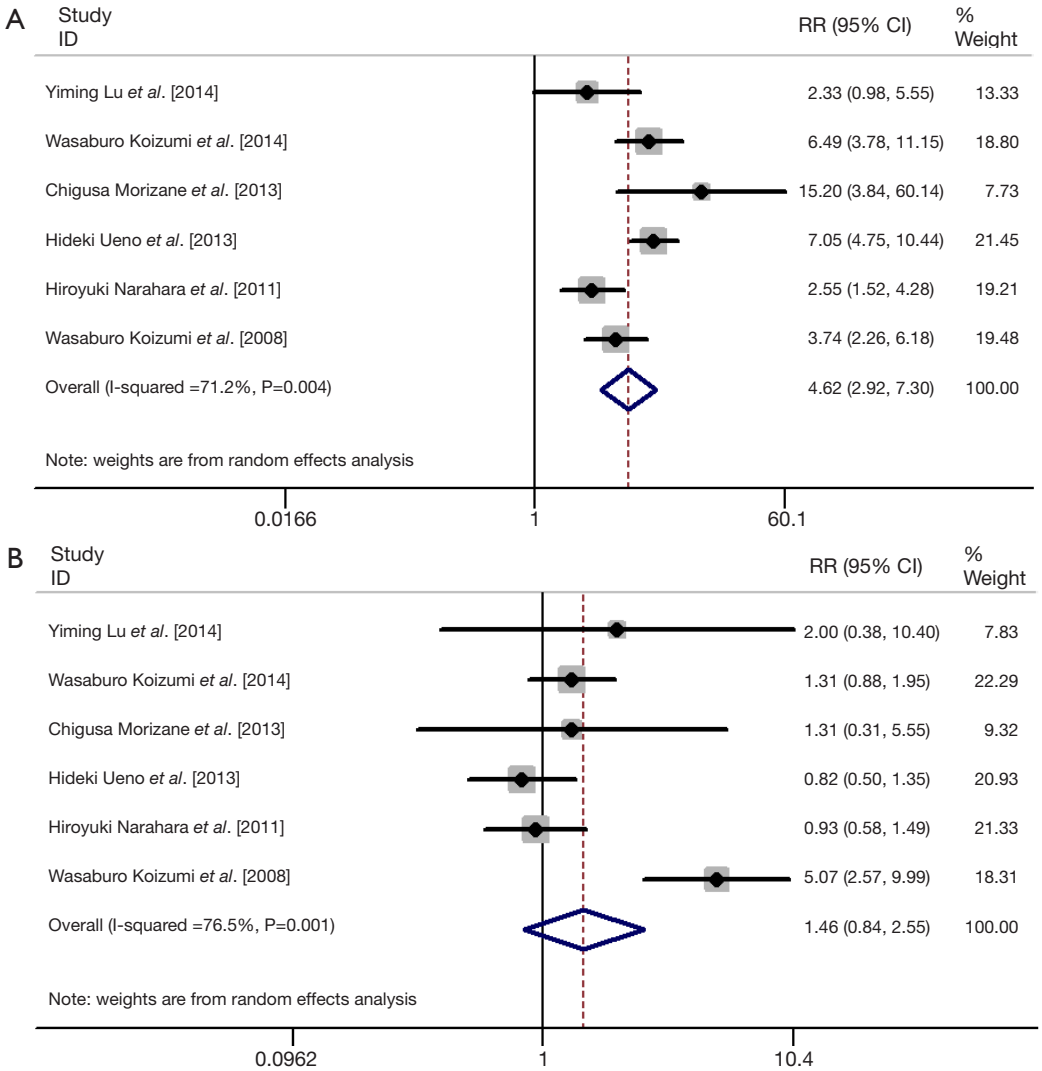


Figure 4 Forest plot for meta-analysis of incidence relative risk of high grade neutropenia (A) and anorexia (B) associated with S-1-based therapy compared with S-1 monotherapy in cancer patients. RR, relative risk; CI, confidence interval.

95% CI: 0.761-0.911, P=0.000, and HR 0.650, 95% CI: 0.540-0.759, P=0.000, respectively). However, the incidence of grade 3/4 adverse effects was also higher in S-1-based therapy than S-1 monotherapy in cancer patients, with RR of neutropenia and anorexia were respectively 4.62 (95% CI: 2.92-7.30) and 1.46 (95% CI: 0.84-2.55).

Our meta-analysis confirmed the previous analysis by Wu *et al*. (7), which also found significantly longer median OS time and median PFS time in AGC patients receiving S-1-based therapy compared with S-1 monotherapy (P=0.000 and P=0.015, respectively), with higher incidence of grade 3/4 neutropenia and anemia.

There are also several limitations in our meta-analysis. Firstly, the heterogeneity was statistically significant in the primary studies. The main reasons may be that definition of the type and grade for adverse events may be different by different investigators and the clinical trial design and modes of treatment may be different. Secondly, a majority of eligible studies were not RCT. The PFS and OS of S-1 monotherapy should be compared with control group with placebo in high-quality RCTs. Thirdly, the HR and CI of OS and PFS in two studies were derived from the methods developed by Parmar *et al*. (31). In some ways, this estimate method may influence the calculated HRs and their CIs. Finally, all of the studies included were in East Asia, including Japan, China, and Korea. The conclusion should

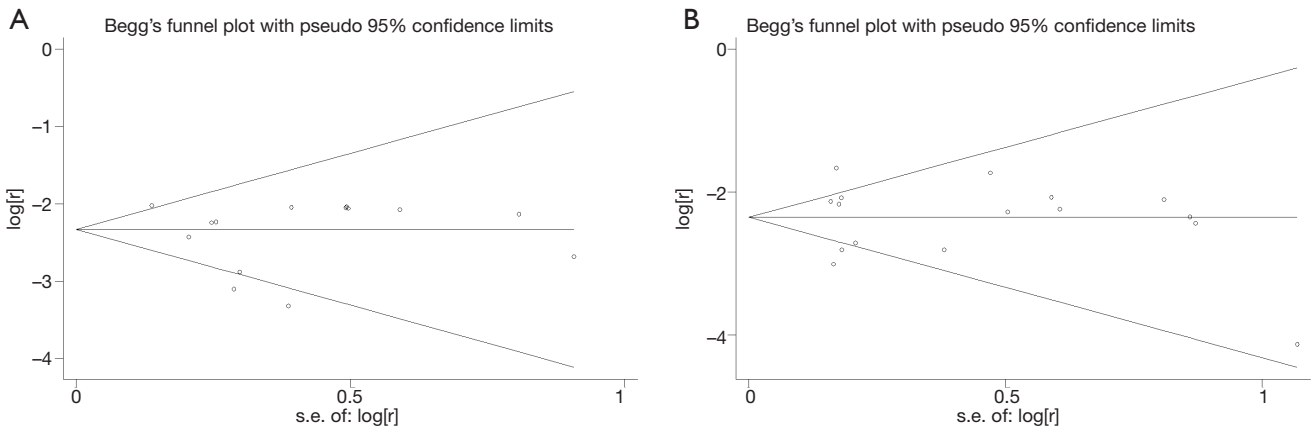


Figure 5 Funnel plot for studies included in this meta-analysis: (A) incidence of grade 3/4 neutropenia; (B) incidence of grade 3/4 anorexia.

be confirmed in Western studies.

In summary, our meta-analysis firstly estimated the high grade adverse effects of S-1 monotherapy in cancer patients, including gastric cancer, pancreatic cancer, NSCLC, colorectal cancer, biliary tract cancer, head and neck cancer and so on. S-1 monotherapy was demonstrated with low incidence of high grade adverse effects, therefore it is well tolerated for majority cancer patients. On the other hand, S-1-based therapy significantly improved OS and PFS compared with S-1 monotherapy, with an increased risk of high grade adverse effects. When the adverse effects can be tolerated, the treatment of S-1-based therapy is better than S-1 monotherapy. Our results should be confirmed with larger RCTs.

Acknowledgements

Funding: This study was supported by the Natural Science Foundation of Jiangsu Province (NO. BK2011658), Clinical Science and Technology Project of Jiangsu Province (NO. BL2013026) and The National Natural Science Foundation of China (NO. 81302032).

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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Cite this article as: Miao Y, Zhan P, Lv T, Song Y. A meta-analysis of safety and efficacy on first-line S-1 therapy in cancer patients. Transl Lung Cancer Res 2015;4(4):487-497. doi: 10.3978/j.issn.2218-6751.2015.07.21

