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ORIGINAL ARTICLE

Fluoropyrimidine-Based Chemotherapy as First-Line Treatment for Advanced Gastric Cancer: a Bayesian Network Meta-Analysis

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Abstract Fluoropyrimidine-based regimens are the most common treatments in advanced gastric cancer. We used a Bayesian network meta-analysis to identify the optimal fluoropyrimidine-based chemotherapy by comparing their relative efficacy and safety. We systematically searched databases and extracted data from randomized controlled trials, which compared fluoropyrimidine-based regimens as first-line treatment in AGC. The main outcomes were overall survival (OS), progression-free survival (PFS), overall response rate (ORR), and grade 3 or 4 adverse events (AEs). A total of 12 RCTs of 4026 patients were included in our network meta-analysis. Pooled analysis showed S-1 and capecitabine had a significant OS benefit over 5-Fu, with hazard ratios of 0.90 (95%CI = 0.81–0.99) and 0.88 (95%CI = 0.80–0.96), respectively. The result also exhibited a trend that S-1 and capecitabine prolonged PFS in contrast to 5-Fu, with hazard ratios of 0.84 (95%CI = 0.66–1.02) and 0.84 (95%CI = 0.65–1.03), respectively. Additionally, all the three fluoropyrimidine-based regimens were similar in terms of ORR and grade 3 or 4 AEs. Compared with regimens based on 5-Fu, regimens based on S-1 or capecitabine demonstrated a significant OS improvement without compromise of AEs as first-line treatment in AGC in Asian population. S-1 and capecitabine can be interchangeable according their different emphasis on AEs.

Keywords Advanced gastric cancer · Fluoropyrimidine · S-1 · Capecitabine · Network meta-analysis

Introduction

Although global incidence of gastric cancer is decreasing, it is still high in eastern Asia [1]. Gastric cancer remains one of the leading causes of deaths worldwide. Moreover, tumors are unresectable at diagnosis for a substantial number of patients [2]. Chemotherapy has been shown to prolong the survival of advanced gastric cancer (AGC) patients and to improve their quality of life [3–5]. Unfortunately, standard chemotherapy regimens for AGC are still not available. Combination chemotherapy containing a fluoropyrimidine (5-Fu, S-1 or capecitabine) plus a platinum agent or paclitaxel are most commonly used [6–9]. Oral fluoropyrimidines including S-1 and capecitabine open up a new era with their simplicity and convenience over the traditional 5-Fu for treatment of AGC [10, 11].

S-1 is an oral fluoropyrimidine derivative consisting of tegafur, gimercacil, and oteracil potassium at a ratio of 1:0.4:1. Tegafur is a prodrug of 5-FU and gradually converted to 5-FU in the liver. Oteracil potassium is a reversible competitive inhibitor of orotate phosphoribosyl transferase, an enzyme that is responsible for gastrointestinal toxicity via its phosphorylation of 5-FU. Therefore, oral administration of S- 1 can achieve a more potent antitumor effect through an increased 5-FU concentration without any additional gastrointestinal toxicity. Flags trial and SC-101 study reveal S-1 has a non-inferior efficacy and better toxicity profile, at least in Asia [9, 12].

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Capecitabine is another oral fluoropyrimidine. It is metabolized primarily in liver and converted in tumor tissues to 5-Fu by the enzyme thymidine phosphorylase. The higher concentrations of thymidine phophorylase in tumor cells than in normal cells contribute to relatively higher target effects. REAL-2 and ML17032 trials prove capecitabine has a superior OS versus 5-Fu in AGC [7, 13].

The optimal regimens based on whether S-1 or capecitabine remain controversial. Two randomized controlled trials (RCTs) directly compare S-1 with capecitabine [14, 15]. However, the two trials fail to dispel that doubts. Recently, He et al. [16] performed a conventional meta-analysis, comparing S-1 with capecitabine in mono or combination regimens, indicating S-1-based chemotherapy had a non-inferior antitumor efficacy and better safety profile. Whereas the number of included studies for comparisons of overall response rate (ORR), progression-free survival (PFS), and overall survival (OS) restricted the potency to draw the conclusion. Evidence of direct comparisons between S-1 and capecitabine is limited, while that of indirect comparisons (S-1 versus 5-Fu and capecitabine versus 5-Fu) is considerable. In addition, network meta-analysis (NMA), an emerging method, enables us to combine all available direct and indirect evidence. [17]

Therefore, we used NMA to evaluate S-1-based, capecitabine-based, and 5-Fu-based regimens by comparing their relative efficacy and safety and to identify the optimal chemotherapy for AGC.

Materials and Methods

Publication Search

We searched PubMed, Web of Science, Medline, Embase, and the Cochrane Library without time limitation to identify RCTs of first-line chemotherapy for AGC. Additional searches through Google Scholar, clinical trial registries, and manual searches through published literatures were used for supplement. The search strategy used both MeSH terms and free-text words to increase sensitivity. The following search terms were used: "gastric/stomach cancer/neoplasm/carcinoma", "first-line/untreated/first line/chemotherapy-naive", "Randomized clinical trial/study", "late/advanced/metastatic/unresectable". Two investigators (LC Zhu and JH Liu) independently identified the eligible reports, and discrepancies were resolved by a third investigator (SL Ma). The study was approved by the Ethics Committee of Hangzhou First People's Hospital.

Selection Criteria

Inclusion criteria are as followings: (1) patients with AGC (unresectable or metastatic) at baseline; (2) RCTs; (3) studies designed to compare different fluoropyrimidine-based regimens (S-1, capecitabine, and 5-Fu) as first-line chemotherapy and not confounded by additional agents or interventions; (4) sufficient data for calculating the efficacy or safety. Exclusion criteria are as followings: (1) letters, editorials, expert opinions, case reports, and reviews. (2) studies without usable data; (3) duplicate publications.

Quality Control

To assess the quality of RCTs, the randomization generation, allocation concealment, blinding of participants, blinding of outcome assessment, and incomplete outcome data were examined. Cochrane Collaboration's tool for assessing risk of bias was used for analyzing RCTs. Any discrepancies were resolved by consensus.

Data Extraction

Two investigators (LC Zhu and JH Liu) independently extracted data from the eligible studies, and disagreements were resolved by discussion with a third investigator (SL Ma). For each studies, the following information was recorded: First author, design type of study, date of publication, sample size, median age, treatment protocol, hazard ratio (HR) with 95 % confidence interval (95%CI) of OS and PFS, ORR, and grade 3 or 4 AEs. We extracted HRs according to the methods raised in a previous publication [18].

Statistical Analysis

OS and PFS were the primary endpoints of this NMA; ORR and Grade 3 or 4 AEs in each arms were the secondary endpoints. Traditional meta-analyses were first conducted. Statistical analyses of HRs for OS and PFS, and the odds ratios for ORR and AEs were calculated by Review Manager Version 5.3 (Revman, the Cochrane Collaboration, Oxford, England). A two-sided *P*-value of <0.05 was considered significant. Heterogeneity across studies was tested by $\chi 2$ test and I^2 statistic along with a forest plot. Statistically significant heterogeneity was defined as a $\chi 2$ *P*-value <0.1 or an I^2 statistic >50 %.

We adopted Bayesian NMA to integrate all direct and indirect treatment comparisons for assessing the effect and safety between three fluoropyrimidine-based regimens and ranked them in sequence [19]. Statistical analyses of HRs for OS and PFS were calculated by WinBUGS version 1.4.3 (MRC Biostatistics Unit, Cambridge, UK) [20] with the model proposed by Wood et al. [21]. Analyses of the odds ratios for ORR and AEs were calculated by ADDIS version 1.16.5 (Van Valkenhoef et al., 2013). Both fixed and random effects models were used. Bayesian deviance information criterion (DIC) statistics were used to compare the two models. The model with a lower DIC, representing a simpler model, was

employed for further analysis [22]. We used non-informative uniform and normal prior distributions to fit the model, yielding 240,000 iterations with a burn-in number of 40,000 iterations and a thin interval of 20 to obtain the estimates. Convergence was assessed using the Brooks-Gelman-Rubin method [23]. The probability of each treatment was assessed by counting the proportion of iterations in the Markow chain of HR ranking in the treatments.

Inconsistency was evaluated between the Bayesian NMA and pairwise meta-analyses. In our study, we used both loop and node-splitting analysis to evaluate inconsistency [24, 25]. Either 95 % CI included 1 in loop analysis or $p < 0.05$ in node-splitting analysis was considered significant inconsistency.

Results

Eligible Studies

As shown in Fig. 1, the electronic search yielded 324 records, and after screening titles and abstracts 13 records remained. We added another 4 articles from references and clinical trial registry. A total of 17 full-text articles were assessed for eligibility. Finally, after excluding 5 articles, a total of 12 RCTs studies [7–9, 12–15, 26–30] were included in the current meta-analysis. 6 of 12 studies had a direct comparison between S-1 and 5-Fu, 4 of them between capecitabine and 5-Fu, and 2 of them between S-1 and capecitabine. Table 1 lists the characteristics of these studies. All the studies were evaluated to be of high quality (Fig 2).

Pair-Wise Meta-Analysis

Supplementary materials (S1-S4 Figs) presents all direct meta-analysis results. Compared with 5-Fu-based chemotherapy, S-1 (HR = 0.89, 95%CI = 0.80–0.98, $p = 0.02$) and capecitabine (HR = 0.85, 95%CI = 0.78–0.94, $p = 0.002$) benefited OS significantly; there was no significant difference between S-1 and capecitabine (HR = 1.09, 95%CI = 0.80–1.48, $p = 0.58$). Capecitabine achieved a significant PFS advantage over 5-Fu (HR = 0.89, 95%CI = 0.79–0.99, $p = 0.03$), while no significant difference was observed between S-1 and capecitabine (HR = 1.04, 95%CI = 0.76–1.41, $p = 0.82$) and between S-1 and 5-Fu (HR = 0.81, 95%CI = 0.63–1.03, $p = 0.09$). Nevertheless, no significant difference of ORR was observed between these regimens (S-1 vs 5-Fu, OR: 1.58, 95%CI: 0.87–2.88, $p = 0.13$; Capecitabine vs 5-Fu, OR: 1.00, 95%CI: 0.57–1.77, $p = 0.99$; S-1 vs Capecitabine, OR: 0.92, 95%CI: 0.50–1.70, $p = 0.80$). All the three regimens were similar in terms of percentage of treatment-related grade 3 or 4 AEs.

Fig. 1 The flow diagram of this meta-analysis

However, S-1 was less frequent compared with 5-Fu in thrombopenia (OR: 0.62, 95%CI: 0.40–0.98, $p = 0.04$) and in stomatitis (OR: 0.22, 95%CI: 0.05–0.90, $p = 0.03$); capecitabine was also less frequent compared with 5-Fu in stomatitis (OR: 0.51, 95%CI: 0.25–1.04, $p = 0.06$).

Network Meta-Analysis of Efficacy

This NMA results were based on both random-effects and fixed-effect models. A model with lower DIC was further adopted for analysis. Figure 3 shows the network of eligible comparisons for efficacy.

Ten studies were included in the NMA of OS. Base on the DIC, the fixed-effects model was adopted for analysis of OS. Compared with 5-Fu-based chemotherapy, S-1 and capecitabine had a significant OS benefit, with hazard ratios of 0.90 (95%CI = 0.81–0.99) and 0.88 (95%CI = 0.80–0.96), respectively; while there was no significant difference between S-1 and capecitabine. The results were in accordance with pairwise meta-analysis. Eight studies reported PFS, and the random effects model was adopted for a lower DIC. Both S-1 and capecitabine did not show significant PFS benefit compared with 5-Fu, and there was also no significant difference between S-1 and capecitabine. Twelve studies reported ORR. We adopted consistency model to analysis ORR because both loop and node-splitting analyses indicated no significant inconsistency. No significant difference of ORR was observed among these regimens. Details are shown in Table 2.

Fig. 4 shows the probability of each treatment being ranked the best, the middle, and the worst. For OS, the cumulative probabilities being ranked the best of each treatment were 64.2 % for capecitabine, 35.8 % for S-1, and 0 % for 5-Fu;

Table 1 Characteristics of literatures included in the meta-analysis

Study	Year	Country	Design	Regimen	N	Age
Ajani	2010	Multi	Phase III	S-1 25 mg/m2 bid d1–21, DDP 75 mg/m2 d1–3, q4w	521	59
				5-Fu 1000 mg/m2 d1–5, DDP 75 mg/m2 d1–3, q4w	508	60
Boku	2009	Japan	Phase III	S-1 40 mg/m2 bid d1–28, q6w	234	64
				5-Fu 800 mg/m2 d1–5, q4w	234	63.5
Cunningham	2008	Multi	Phase III	5-Fu 200 mg/m2 d1–21, Epi 50 mg/m2 d1, DDP 60 mg/m2 d1, q3w	249	65
				Cap 625 mg/m2 bid d1–21, Epi 50 mg/m2 d1, DDP 60 mg/m2 d1, q3w	241	64
				5-Fu 200 mg/m2 d1–21, Epi 50 mg/m2 d1, L-OHP 130 mg/m2 d1, q3w	235	61
				Cap 625 mg/m2 bid d1–21, Epi 50 mg/m2 d1, L-OHP 130 mg/m2 d1, q3w	239	62
Huang	2013	China	Phase II	S-1 40-60 mg bid d1–14, Taxol 60 mg/m2 d1,8,15, q4w	119	56
				5-Fu 500 mg/m2 d1–5, Taxol 60 mg/m2 d1,8,15, q4w	110	54
Jin	2008	China	Phase III	S-1 80 mg/m2 d1–21, DDP 60 mg/m2 d8, q5w	74	56.5
				5-Fu 600 mg/m2 d1–5, DDP 20 mg/m2 d1–5, q4w	73	58
Kang	2009	Multi	Phase III	Cap 1000 mg/m2 bid d1–14, DDP 80 mg/m2 d1, q3w	160	56
				5-Fu 800 mg/m2 d1–5, DDP 80 mg/m2 d1, q3w	156	56
Kim	2012	Korea	Phase II	S-1 40 mg/m2 bid d1–14, L-OHP 130 mg/m2 d1, q3w	65	60
				Cap 1000 mg/m2 bid d1–14, L-OHP 130 mg/m2 d1, q3w	64	61
Lee	2008	Korea	Phase II	S-1 40-60 mg/m2 bid d1–28, q6w	45	71
				Cap 1250 mg/m2 bid d1–14, q3w	46	71
Nishikawa	2012	Japan	Phase II	5-Fu 800 mg/m2 d1–5, q4w → Taxol 80 mg/m2 d1,8,15, q4w	38	67
				S-1 80 mg/m2 d1–28, q6w → Taxol 80 mg/m2 d1,8,15, q4w	40	68
				5-Fu 600 mg/m2 d1–5, Taxol 80 mg/m2 d8,15,22, q4w	39	67.3
				S-1 80 mg/m2 d1–14, Taxol 50 mg/m2 d1,8, q3w	40	66.6
Ocvirk	2012	Slovenia	Phase II	Cap 825 mg/m2 bid d1–14, Epi 50 mg/m2 d1, DDP 60 mg/m2 d1, q3w	40	55.6
				5-Fu 200 mg/m2 d1–14, Epi 50 mg/m2 d1, DDP 60 mg/m2 d1, q3w	45	54.7
Sanofi	2011	Multi	Phase II	Cap 625 mg/m2 bid d1–21, Doc 50 mg/m2 d1, L-OHP:100 mg/m2 d1, q3w	86	59
				5-Fu 2400 mg/m2/46 h, Doc:40 mg/m2 d1, L-OHP:85 mg/m2 d1, q2w	89	57.9
Xu	2013	China	Phase III	S-1 40 mg/m2 bid d-21, DDP:20 mg/m2 d1–4, q5w	120	-
				5-Fu 800 mg/m2 d1–5, DDP:20 mg/m2 d1–4, q4w	116	-

DDP cisplatin, *Epi* epirubicin, *Cap* capecitabine, *L-OHP* oxaliplatin, *Taxol* paclitaxel, *Doc* docetaxel

for PFS, the cumulative probabilities were 51.6 % (S-1), 47.6 % (capecitabine), and 0.01 % (5-Fu); for ORR, they were 72.0 % (S-1), 23.0 % (capecitabine), and 5.0 % (5-Fu).

Grade 3 or 4 Advent Events

Table 3 summarizes the grade 3 or 4 AEs included in this study. All the three regimens were similar in terms of percentage of treatment-related grade 3 or 4 AEs. S-1 showed least frequent in thrombopenia (63.0 %), vomiting (67.0 %), and stomatitis (77.0 %); while capecitabine exhibited least frequent with anemia (69.0 %), leucopenia (66.0 %), and nausea (57.0 %); 5-Fu was best in neutropenia (48.0 %), diarrhea (81.0 %) and fatigue (78.0 %). S-1 showed most frequent in anemia (54.0 %), leucopenia (69.0 %), and diarrhea (55.0 %); while capecitabine exhibited most frequent with neutropenia (54.0 %) and fatigue (86.0 %); 5-Fu was worst in thrombopenia (54.0 %), nausea (81.0 %), vomiting (70.0 %), and stomatitis (83.0 %).

Discussion

Twelve RCTs of 4026 patients were included in our NMA, which were based on three fluoropyrimidine-based regimens as first-line treatment for AGC. We aimed to integrate data on fluoropyrimidine-based chemotherapy to choose a regimen that balances efficacy and safety for treating AGC. This study adopted Bayesian NMA to compare efficacy and safety of S-1-, capecitabine-, and 5-Fu-based chemotherapy for AGC. Our results demonstrated that S-1- and capecitabine-based regimens showed similar efficacy in terms of OS, PFS, and ORR. Both had a benefit of OS and PFS over 5-Fu-based regimens. The three fluoropyrimidine-based chemotherapy each exhibited advantage in different grade 3 or 4 AEs.

5-Fu-based regimen is one of the most common regimens in AGC [6, 31–35], whereas it is given as a continuously infusion, which can be associated with inconvenient, infection, and thrombosis. Therefore, new oral fluoropyrimidines

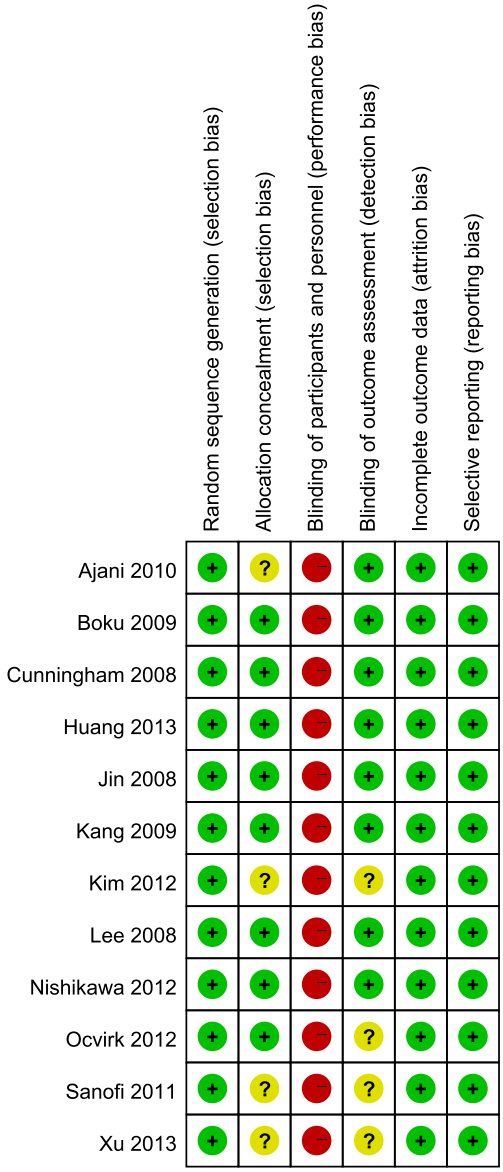

Fig. 2 Risk of Bias Summary of all RCTs. *Green* represents low risk of bias, *red* represents high risk of bias, *yellow* represents unclear risk of bias

are developed. S-1 and capecitabine overcome some disadvantages of 5-Fu by oral administration. In the JCOG 9912 trial [9], in which S-1 alone was compared with 5-Fu alone and irinotecan plus cisplatin, S-1 alone showed non-inferiority to 5-Fu and irinotecan plus cisplatin in AGC. Compared with 5-Fu plus cisplatin, S-1 plus cisplatin exhibited fewer toxic effects without compromising efficacy in the FLAGS trial [8]. In the REAL-2 trial [7] and ML17032 trial [13], administration of capecitabine demonstrated non-inferiority compared to 5-Fu. In addition, another meta-analysis based on these two trials showed a significant improvement of OS in capecitabine-based regimens over 5-Fu-based regimens [36]. Lee et al. [14] conducted a phase II RCT to compare S-1 alone with capecitabine alone in elder patients with AGC, showing a commensurate efficacy and safety between two regimens.

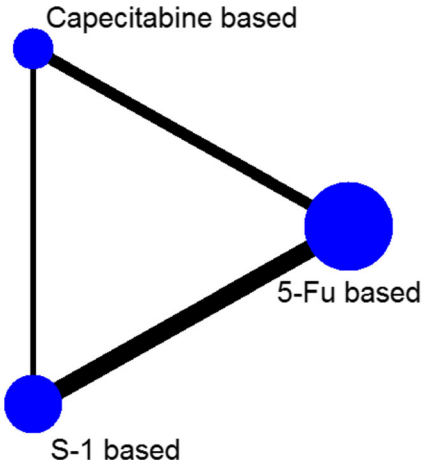

Fig. 3 Network of eligible comparisons for the network meta-analysis for efficacy. The width of the lines is proportional to the number of trials comparing every pair treatments, and every node is proportional to the number of randomized participants (sample size)

Another phase II RCT [15] from Korea demonstrated a similar results comparing S-1 plus oxaliplatin with capecitabine plus oxaliplatin in AGC.

Our results showed that 5-Fu-based regimens were inferior to both S-1- and capecitabine-based regimens in terms of OS, while there was no significant difference between S-1- and capecitabine-based regimens. The results were similar with previous meta-analyses [16, 36, 37]. The result of comparison between capecitabine and 5-Fu was a little bit different from the meta-analysis conducted by Wagner et al. [38], only one RCT included in that study might explain the difference. Divergent outcomes were shown in our analysis of PFS. The

Table 2 Efficacy of the three fluoropyrimidine based regimens in network meta-analysis

S-1	DIC in Fixed model = −9.6	
	DIC in Random model = −7.7	
1.03 (0.90–1.16) 1.04 (0.87–1.24)	Capecitabine	OS
0.90 (0.81–0.99) 0.89 (0.78–1.02)	0.88 (0.80–0.96) 0.86 (0.73–0.99)	5-Fu
S-1	DIC in Fixed model = −2.9	
	DIC in Random model = −4.6	
1.08 (0.89–1.30) 1.07 (0.76–1.45)	Capecitabine	PFS
0.87 (0.79–0.97) 0.84 (0.66–1.02)	0.88 (0.79–0.98) 0.84 (0.65–1.03)	5-Fu
S-1	Consistency Model	
	Inconsistency Model	
1.28 (0.60–2.75) 1.15 (0.44–2.93)	Capecitabine	ORR
1.46 (0.81–2.63) 1.51 (0.83–2.74)	1.13 (0.58–2.25) 1.08 (0.53–2.17)	5-Fu

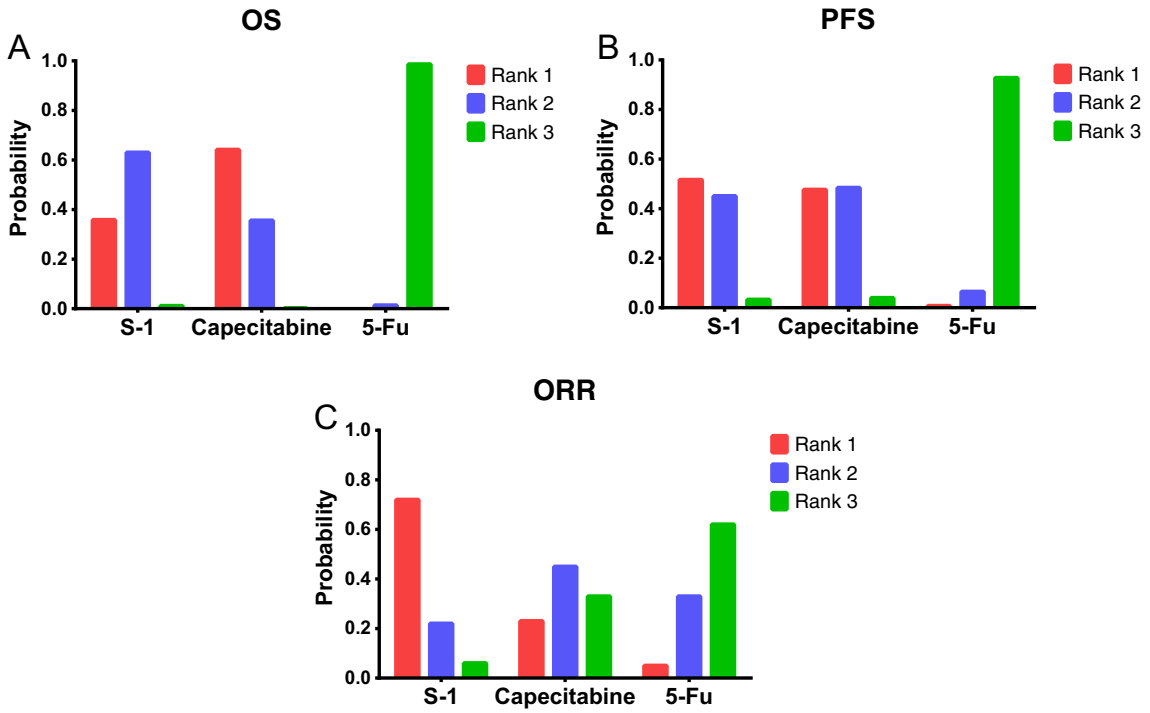

Fig. 4 Probabilities of each treatment ranking of OS, PFS and ORR. *Rank 1* represents best, *Rank 3* represents worst

fixed effect model showed a PFS benefit with S-1 and capecitabine over 5-Fu; though the upper limit of 95%CI of PFS was close to 1, the random effect model did not showed a significant difference at a p level of <0.05. In our pairwise meta-analysis, capecitabine-based regimens achieved a significant PFS advantage over 5-Fu-based regimens. There was also no significant difference of PFS between S-1- and capecitabine-based regimens. It showed a consistency with

Table 3 Ranking probabilities and odd ratios of the three fluoropyrimidine based regimens in network meta-analysis of grade 3 or 4 advent events

	S-1			Capecitabine			5-Fu		
	Rank 1	Rank 2	Rank 3	Rank 1	Rank 2	Rank 3	Rank 1	Rank 2	Rank 3
	OR:95%CI (S-1 vs 5-Fu)			OR:95%CI (Cap vs 5-Fu)			OR:95%CI (S-1 vs Cap)		
Anemia	0.54	0.33	0.13	0.14	0.17	0.69	0.31	0.50	0.18
	1.09 (0.55–2.30)			0.78 (0.31–1.87)			1.40 (0.56–3.84)		
Leucopenia	0.69	0.24	0.07	0.13	0.21	0.66	0.18	0.55	0.27
	1.41 (0.58–3.91)			0.73 (0.20–2.64)			1.93 (0.51–8.19)		
Neutropenia	0.33	0.36	0.31	0.54	0.25	0.21	0.13	0.39	0.48
	1.12 (0.52–2.52)			1.29 (0.54–3.19)			0.88 (0.31–2.46)		
Thrombopenia	0.14	0.24	0.63	0.33	0.4	0.27	0.54	0.36	0.11
	0.74 (0.38–1.95)			0.90 (0.38–2.26)			0.82 (0.35–2.61)		
Diarrhea	0.55	0.38	0.07	0.44	0.45	0.12	0.02	0.17	0.81
	2.22 (0.64–9.36)			2.01 (0.57–11.42)			1.11 (0.16–5.48)		
Nausea	0.12	0.47	0.41	0.07	0.36	0.57	0.81	0.17	0.02
	0.72 (0.38–1.18)			0.72 (0.38–1.18)			1.07 (0.57–2.26)		
Vomiting	0.05	0.28	0.67	0.26	0.44	0.31	0.7	0.28	0.02
	0.65 (0.30–1.17)			0.81 (0.36–1.64)			0.82 (0.30–2.07)		
Fatigue	0.12	0.68	0.2	0.86	0.12	0.02	0.02	0.21	0.78
	1.39 (0.59–4.98)			2.82 (0.90–11.43)			0.51 (0.15–1.88)		
Stomatitis	0.03	0.2	0.77	0.14	0.64	0.22	0.83	0.16	0.01
	0.18 (0.04–1.08)			0.44 (0.06–2.75)			0.41 (0.04–6.55)		

Rank 1 represents worst, *Rank 3* represents best. *Cap*, Capecitabine

previous meta-analyses [16, 36]. For ORR, no significant difference was observed among these regimens. One recent meta-analysis [39] compared S-1 with capecitabine proving a similar result. Another recent meta-analysis [40] compared efficacy of S-1 with capecitabine and S-1 with 5-Fu, and the outcome was in accordance with ours. As expected, 5-Fu-based regimens ranked worst for OS, PFS, and ORR. As for S-1 and capecitabine, the former ranked superior in PFS and ORR, while the latter ranked superior in OS.

With regard to safety profile, none of all the three regimens was dominant over the other on treatment- related grade 3 or 4 AEs. Despite that, we can still get some hints from Table 3. For example, S-1 showed least frequent in stomatitis, patient with mild stomatitis might prefer administration of S-1 rather than 5-Fu for its worst ranking in stomatitis. Patient being susceptible to anemia might prefer administration of capecitabine for its best ranking in anemia. Of course, the probability of treatment ranking is a complement not a substitute for clinical decisions.

Nevertheless, there are several limitations in the study. All information was extracted from published data, which might result in publication and reporting bias. In addition, missing information on certain endpoints could have affected the analysis without access to individual patient data, e.g., OS was not available in the study by Huang et al. [27] and Sanofi et al. [30]. Furthermore, insufficient information about allocation concealment and blinding in some included trials might weaken the strength of findings [41]. Notably, most of our included S-1 studies were performed on Asian populations. Previous study indicated Caucasian and Asian population had different pharmacokinetic parameters on S-1. [42] This difference may attribute to different polymorphisms in the CYP2A6 gene. [43, 44] CYP2A6 enzyme was supposed as a key enzyme in conversion of tegafur to 5-Fu. [45] *Ajani* et al. [42] found Caucasian population achieved a higher area under curve (AUC) of 5-Fu than Asian in the comparable dose range of S-1 as more rapid catabolism of tegafur to 5-Fu. While concentration of 5-Fu in the plasma has a direct correlation with toxicity of S-1. The toxicity limits Caucasian population given high dose of S-1 as Asian population. Nevertheless, a phase III study mainly performed on Caucasian population reported Cisplatin/S-1 resulted significantly reduced severe AEs with a similar OS compared with cisplatin/5-Fu.

Conclusion

Our NMA showed that there was significant OS improvement in S-1- and capecitabine-based regimens compared with 5-Fu-based regimens as first-line treatment for AGC at least in Asian population. For Caucasian population, more studies were needed to draw a conclusion. Compared with 5-Fu, a trend was found that S-1- and capecitabine-based regimens prolonged PFS, though the difference was not significant. S-1-based chemotherapy showed similar efficacy and safety profile compared with capecitabine-based chemotherapy. All the three fluoropyrimidine-based regimens were similar in terms of ORR and grade 3 or 4 AEs. We recommended S-1 and capecitabine can be interchangeably according to their different emphasis on AEs.

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Compliance with Ethical Standards

Conflict of Interest All authors declare that there is no conflict of interests.

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