

WJG 20th Anniversary Special Issues (8): Gastric cancer**Non-platinum-based chemotherapy for treatment of advanced gastric cancer: 5-fluorouracil, taxanes, and irinotecan**

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this review focuses on the efficacy and tolerability of non-platinum-based chemotherapy for patients with AGC.

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Core tip: Although platinum-based chemotherapy is adopted widely nowadays in spite of numerous side effects, there is still no standard treatment for palliative chemotherapy of advanced gastric cancer. The current review assessed the efficacy and tolerability of non-platinum-based chemotherapy as first-line palliative treatment in patients with inoperable advanced gastric cancer. The results showed that non-platinum-based chemotherapy including 5-fluorouracil, taxanes, and irinotecan, would seem to be as effective and tolerable as traditional platinum-based chemotherapy.

Abstract

Despite numerous advances in treatment options, advanced gastric cancer (AGC) remains a major public health issue and the leading cause of cancer-related deaths. Cisplatin is one of the most effective broad-spectrum anticancer drugs for AGC and a doublet combination regimen of either cisplatin-based or 5-fluorouracil (5FU)-based chemotherapy is generally used for treatment of patients with AGC. However, there is still no consensus on the best regimen for treating AGC. Recently, various new chemotherapeutic agents, including oral 5FU, taxanes, and irinotecan, have been identified as improving the outcomes for AGC when used as a single agent or in combination with non-platinum chemotherapy. Nonetheless, it is still unclear whether non-platinum-based chemotherapy is a viable treatment option for patients with AGC. Accordingly,

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INTRODUCTION

Advanced gastric cancer (AGC) is a major public health issue and the leading cause of cancer-related deaths, with a 5-year survival of only 20%^[1-3]. Despite numerous advances in treatment options, the prognosis for AGC remains dismal, as most patients are in an advanced or

inoperable stage at the time of diagnosis. One of the most important treatment modalities is systemic chemotherapy. A recent phase III trial showed that the addition of trastuzumab to cisplatin-based chemotherapy significantly improved the survival of patients with human epidermal receptor 2 (HER2)-positive AGC^[4]. However, the frequency of HER2 overexpression is low (10%-20%), and there is no widely accepted first-line treatment for HER2-negative AGC.

Cisplatin is a small-molecule platinum compound forming intrastrand cross-links that activate the apoptotic pathway, resulting in cell death^[5]. Cisplatin is also one of the most effective broad-spectrum anticancer drugs for AGC. Generally, a doublet combination regimen of either cisplatin-based or 5-fluorouracil (5FU)-based chemotherapy is used for treating AGC^[6]. While a cisplatin-based combination has been found to be marginally superior to other combinations, the benefit is still disappointing, with a response rate below 50% and high rate of toxicity^[7].

The significant toxicity of cisplatin, which often results in nausea, vomiting, nephrotoxicity, and neurotoxicity, can also affect the final treatment outcomes and quality of life as the majority of patients present in an advanced stage. Plus, the effect of cisplatin-based chemotherapy has been found to vary depending on the tumor biology, where resistance markedly reduces its clinical effectiveness^[8]. Interestingly, the introduction of new agents, such as oral 5FU, taxanes, and irinotecan, has provided improved treatment outcomes for patients with AGC. In a recent meta-analysis by Chen *et al.*^[9], combination regimens with such agents achieved a similar response rate and overall survival to platinum-based regimens. The toxicity of non-platinum-based regimens is also significantly lower in terms of hematologic toxicity, vomiting, and neurotoxicity. Nonetheless, it is still unclear whether non-platinum-based chemotherapy is a viable treatment option for patients with AGC. Accordingly, this review focuses on the efficacy and tolerability of non-platinum-based chemotherapy for patients with AGC.

ROLE OF PLATINUM-BASED CHEMOTHERAPY IN AGC

Platinum-based doublet chemotherapy, typically cisplatin in combination with either infused 5FU or an oral 5FU, such as S-1 or capecitabine, is current standard practice in many countries^[1]. In a randomized phase III trial (SPIRITS trial)^[10], 298 patients with AGC were randomized to S-1 plus cisplatin or S-1 alone. Median progression-free survival (PFS) (6.0 mo *vs* 4.0 mo) and overall survival (OS) (13.0 mo *vs* 11.0 mo) were significantly longer in the combination group. The response rate was also higher with S-1 (54% *vs* 31%). Based on this trial, the S-1 plus cisplatin combination regimen has been established as a standard treatment for AGC in Japan. Two phase III trials have compared the efficacy and safety of capecitabine-based and 5FU-based combinations. In Western countries, the

REAL-2 trial was a randomized multicenter phase III study comparing capecitabine with 5FU, and oxaliplatin with cisplatin in 1003 patients with AGC^[11]. Although 30% of patients had an esophageal cancer, results from this study suggest that capecitabine and oxaliplatin are as effective as 5FU and cisplatin, respectively. Another phase III randomized trial (ML17032 trial) evaluated the combination of capecitabine and cisplatin *vs* the combination of 5FU and cisplatin in patients with AGC^[12]. The capecitabine and cisplatin combination met the primary endpoint of non-inferiority of PFS (5.6 mo *vs* 5.0 mo). Median OS (10.5 mo *vs* 9.3 mo) and severity of adverse events were comparable in both groups. Consequently, oral 5FU (capecitabine or S-1) and a platinum-based combination has been widely accepted as one of the first choices worldwide for treatment of patients with AGC.

SINGLE-AGENT CHEMOTHERAPY

A previous meta-analysis demonstrated a significant survival benefit related to combination chemotherapy when compared with a single agent^[3]. However, in most previous studies, 5FU has only been evaluated as single-agent chemotherapy. In addition, several new drugs, such as oral 5FU, taxanes, and irinotecan, have also been evaluated only as single agents in terms of their efficacy and tolerability when treating AGC.

5FU (intravenous)

In the early 1980s, 5FU alone was evaluated as an active single agent for patients with AGC^[13]. Subsequently, 5FU in combination with leucovorin was also investigated^[14,15]. However, while these studies reported a 19%-48% objective response rate and tolerable toxicity profiles, more than half the patients had other types of gastrointestinal malignancies. A randomized phase II trial by Barone *et al.*^[16] compared a combination of 5FU and leucovorin with a cisplatin-containing regimen (cisplatin, etoposide, and epirubicin), where the median response duration was 8.8 and 8.3 mo, respectively. Thereafter, 5FU alone has been used as the reference arm in randomized phase III trials. The North Central Cancer Treatment Group compared three arms (5FU alone *vs* 5FU plus adriamycin *vs* 5FU, adriamycin, and methotrexate), however, there was no significant difference in the treatment outcomes^[17]. Similarly, in Japan, two randomized trials found no survival advantage between cisplatin-based chemotherapy (5FU plus cisplatin or irinotecan plus cisplatin) and FU alone (7.1 mo *vs* 7.3 mo; 10.8 mo *vs* 12.3 mo)^[18,19]. Although cisplatin-based chemotherapy produced a higher response rate and PFS, 5FU alone was associated with less toxicity.

5FU (oral)

Oral 5FU agents, such as capecitabine and S-1, are commonly used for AGC and have several advantages, including the possibility of continuous exposure to 5FU at the tumor site and minimized systemic exposure to 5FU,

thereby reducing the toxicity and improving the convenience and quality of life^[20,21]. The activity of capecitabine has already been tested in phase II studies, and resulted in a response rate of 6%-32%^[22]. In two early phase II studies conducted in Korea and Japan, capecitabine showed a median survival of 8-10 mo and response rate of approximately 20%-30%^[23,24]. Meanwhile, in another study with 704 patients, Boku *et al*^[18] demonstrated the non-inferiority of S-1 alone, and superiority of irinotecan plus cisplatin over 5FU alone. For the primary endpoint, the PFS for S-1 was not inferior to that for 5FU (4.2 mo *vs* 2.9 mo, $P < 0.001$), and there was even a trend suggesting the superiority of S-1 over 5FU alone. The two arms were also comparable as regards adverse events, meaning that S-1 is an acceptable alternative to 5FU alone. Another important factor is that these two agents can be considered as an option for elderly patients or patients with a poor performance status. In a phase II trial of S-1 in patients with a poor performance status and intolerance to combination chemotherapy, the results showed that S-1 was an active and safe drug with a response rate of 12%^[25]. Meanwhile, capecitabine was directly compared with S-1 in a randomized phase II trial of 91 elderly patients^[26]. In this case, the two agents (capecitabine *vs* S-1) were found to be comparable in terms of the response rate (27.2% *vs* 28.9%), median time to progression (4.7 mo *vs* 4.2 mo), OS (9.5 mo *vs* 8.2 mo), and treatment-related toxicity. Therefore, the above findings suggest that oral 5FU agents can be used for patients where platinum agents are contraindicated.

Taxanes

Taxanes (paclitaxel or docetaxel) disrupt the microtubule function and inhibit the process of cell division, and have shown encouraging activity in the treatment of AGC^[27,28]. Several studies have already investigated the use of paclitaxel monotherapy for AGC and found response rates ranging from 17% to 28%^[28]. When investigating the efficacy of paclitaxel every 3 wk as first-line treatment for AGC patients, Ajani *et al*^[29] found that a dose of 200 mg/m² was generally well tolerated, produced a response rate of 17%, and the median survival was 8 mo. Meanwhile, when using a weekly dose of paclitaxel of 80 mg/m², the response rate was 17.6% and the median survival was 7.3 mo^[30]. Docetaxel monotherapy has also been assessed for AGC patients in several phase II studies^[31]. When using a dose of 60-100 mg/m² every 3 wk^[31-33], the response rate was 15%-25% and the median survival ranged from 7.5 to 11.0 mo. While the most common adverse event was neutropenia, the incidence of neutropenic fever was very low. Therefore, despite the varying response rates, the overall outcome for taxanes was similar to that observed for most single conventional drugs, making taxanes an appropriate option for AGC.

Irinotecan

Irinotecan prevents DNA from unwinding by inhibiting topoisomerase I^[34]. Multiple trials have already shown

good tolerance and promising results when using irinotecan as a single therapy for AGC, including response rates from 14% to 20% and a median survival of approximately 7 mo^[35,36]. As regards toxicity, the most common grade 3-4 toxicities were diarrhea (20%-30%) and neutropenia (23%-38.5%). Thus, despite a slightly higher response rate than with conventional agents, the toxicity of irinotecan remains a concern. Nonetheless, irinotecan can still be considered as an alternative single agent when a platinum-based therapy cannot be delivered.

COMBINATION CHEMOTHERAPY

In clinical trials, various new chemotherapeutic agents, including oral 5FU, taxanes, and irinotecan, have been identified as improving the outcomes for AGC when used in combination with non-platinum doublet chemotherapy.

For example, when studying the combination of 5FU plus anthracycline in conjunction with mitomycin or methotrexate, the initial reports showed high response rates of 30% to 60% and significantly improved survival with the addition of anthracyclines when compared with cisplatin and 5FU alone. However, the survival benefits were not consistent in a meta-analysis^[2,6,17,37-39]. Meanwhile, oral 5FU plus cisplatin or oxaliplatin combinations have been found to be more effective than the conventional regimen of cisplatin with 5FU alone^[12,13]. Thus, the questionable efficacy of adding anthracyclines has resulted in a worldwide decrease in their use.

Various combinations of oral 5FU agents (capecitabine or S-1) and taxanes or irinotecan have already been used in experimental models and, despite the absence of platinum agents, such combinations have been found to enhance the anticancer activity and overcome the resistance to each agent^[40-42]. Thus, several phase II studies have since investigated these combinations (Table 1), including capecitabine plus taxanes, capecitabine plus irinotecan, S-1 plus taxanes, and S-1 plus irinotecan, as the backbone of combination chemotherapy without a platinum agent. The results were promising, with an overall response rate of 37%-52%, and median overall survival of 8-16 mo^[43-55]. Although a direct comparison is difficult due to the limitation of randomized phase II studies, three studies demonstrated comparable outcomes to cisplatin-containing chemotherapy in terms of the response rate, survival, and toxicity^[44,46,54]. The combination of docetaxel and irinotecan without cisplatin was also tested in a phase II trial, where doses of docetaxel 40 mg/m² per day and irinotecan 100 mg/m² per day on a 3-wk cycle provided an acceptable safety profile and modest activity with a response rate of 26%^[56]. In addition, the combination of irinotecan, 5FU, and leucovorin (FOLFIRI) has been shown to be active and well tolerated in patients with AGC^[57,58]. Therefore, based on the results of these trials, an irinotecan-containing regimen can be considered as a suitable alternative to a platinum combination.

A recent meta-analysis by Chen *et al*^[9] evaluated the efficacy and tolerability of platinum *vs* non-platinum che-

Table 1 Selected phase II and III trials of first-line non-platinum-based chemotherapy for patients with advanced gastric cancer

Ref.	Year	Phase	Tx	Dose (mg/m ² per day)	Cycle	Patients (n)	RR	Median TTP/ TTF/PFS (mo)	Median OS (mo)	P value for OS
Vanhoefer <i>et al</i> ^[37]	2000	III	FAM	(5FU: 1500, A: 30, M: 1500)	(D1, D1, and D15, 4 wk)	85	12%	3.3	6.7	-
			FC	(F: 1000, C: 100)	(D1-5 and D2, 4 wk)	81	20%	4.1	7.2	0.77
			ELF	(L: 300, E: 120, F: 500)	(D1-5, 3 wk)	79	9%	3.3	7.2	0.73
Boku <i>et al</i> ^[18]	2009	III	F	F: 800	D1-5, 4 wk	234	-	2.9	10.8	-
			IC	(I: 70, C: 80)	(D1,15 and D1, 4 wk)	236	-	4.8	12.3	0.055 ¹
			S	S: 80	D1-28, 6 wk	234	-	4.2	11.4	< 0.001 ²
Ohtsu <i>et al</i> ^[19] (JCOG 9205)	2003	III	F	F: 800	D1-5, 4 wk	105	11.4%	1.9	7.1	-
			FC	(F: 800, C: 20)	(D1-5 and D1-5, 4 wk)	105	34.3%	3.9	7.6	0.34
			U/T ³	U/T: 750	-	70	8.6%	2.4	6.0	0.11
Kim <i>et al</i> ^[59]	2005	II	DX	D: 75 X: 2000	D1, 3 wk D1-14, 3 wk	32	43.8%	5.1	8.4	-
			DX	D: 75 X: 1650	D1, 3 wk D1-14, 3 wk	44	39%	4.2	9.4	-
Giordano <i>et al</i> ^[60] (NCCTG)	2006	II	DX	D: 75 X: 1650	D1, 3 wk D1-14, 3 wk	44	39%	4.2	9.4	-
Jeung <i>et al</i> ^[54]	2011	II	DS	(D: 35, S: 70)	(D1, 8 and D1-14, 3 wk)	39	46%	7.3	16.0	0.019
			(random) DC	(D: 35, C: 35)	(D1, 8 and D1, 8, 3 wk)	41	24%	4.8	8.2	-
Park <i>et al</i> ^[50]	2006	II	PF	(P: 175, F: 500)	(D1 and D1-5, 3 wk)	38	42%	3.6	9.9	-
			(random) DF	(D: 75, F: 500)	(D1 and D1-5, 3 wk)	39	33%	4.2	9.3	-
Mochiki <i>et al</i> ^[44]	2012	II	SP	(S: 80, P: 60)	(D1-14 and D1, 8, 15, 4 wk)	42	52.3%	9.0	16.0	0.084
			(random) SC	(S: 80, C: 60)	(D1-21 and D8, 5 wk)	41	48.7%	6.0	17.0	-
Pozzo <i>et al</i> ^[51]	2004	II	ILF	(I: 80, L: 500, F: 2000)	(D1, weekly, 6 wk)	74	42.4%	6.5	10.7	0.0018
			(random) IC	(I: 200, C: 60)	(D1 and D1, 3 wk)	72	32.1%	4.2	6.9	-
Narahara <i>et al</i> ^[48] (GC0301/TOP-002)	2011	III	IS	(S: 80, I: 80)	(D1-21, 5 wk, D1 and 15, 5 wk)	164	41.5%	4.5	12.8	0.233
			S	S: 80	D1-28, 6 wk	162	26.9%	3.6	10.5	-
Moehler <i>et al</i> ^[46]	2010	II	IX	(I: 250, X: 2000)	(D1 and D1-14, 3 wk)	57	37.7%	4.2	10.2	-
			(random) CX	(C: 80, X: 2000)	(D1 and D1-14, 3 wk)	55	42.0%	4.8	7.9	-
Oh <i>et al</i> ^[49]	2007	II	IX	(I: 130, X: 3500)	(D1,15 and D1-15, 3 wk)	55	43.6%	5.0	11.0	-
Baek <i>et al</i> ^[55]	2006	II	IX	(I:100, X: 2000)	(D1, 8 and D1-14, 3 wk)	41	46.3%	5.1	8.6	-
Bouché <i>et al</i> ^[57] (FFCD 9803)	2004	II	LF	(L: 200, F: 400/600)	(D1-2, 2 wk)	45	13%	3.2	6.8	-
			LFC	(L: 200, F: 400/600, C: 50)	(D1-2, 2 wk)	44	27%	4.9	9.5	-
			LFI	(F: 200, F: 400/600, I: 180)	(D1-2, 2 wk)	45	40%	6.9	11.3	-
Dank <i>et al</i> ^[58]	2008	III	IFL	(I: 80, L: 500, F: 2000)	(D1, weekly, 6 wk)	172	31.8%	5.0	9.0	0.53
			CF	(C: 100, F:1000)	(D1 and D1-5, 4 wk)	165	25.8%	4.2	8.7	-

¹Superiority compared to 5-fluorouracil (5FU) alone; ²Non-inferiority compared to 5FU alone; ³With weekly bolus infusion of mitomycin 5 mg/m². Tx: Treatment; TTP: Time to progression; TTF: Time to treatment failure; PFS: Progression-free survival; OS: Overall survival; F: 5FU; A: Adriamycin; M: Methotrexate; C: Cisplatin; E: Etoposide; L: Leucovorin; I: Irinotecan; S: S-1; U/T: Uracil and tegafur; D: Docetaxel; X: Capecitabine; P: Paclitaxel.

mootherapy as a first-line palliative treatment for patients with inoperable AGC. Based on 3680 patients in 27 trials, where 8 trials used pooled estimates for OS, the final hazard ratio for OS of 1.07 (95%CI: 0.88-1.30) showed no significant difference between the platinum-based and the non-platinum-based therapies containing new-generation agents. However, the occurrence of most adverse events was higher in the platinum-arm, except for diarrhea, and most importantly, the toxic death rate and nephrotoxicity were much higher in the platinum arm. Therefore, the combination regimens including new-generation agent showed a similar impact on survival and better tolerability.

CONCLUSION

Cisplatin-based and 5FU-based combinations are both widely used for AGC, yet there is no consensus on the best regimen. Predicting the response to each chemotherapeutic agent is difficult and the treatment outcomes vary in clinical studies. In addition, when determining the appropriate chemotherapy, assessment of the sever-

ity of the disease and the toxicity related to a particular chemotherapy are both essential to improve outcomes and relieve substantial toxicity. In the current review, newer agents, such as oral 5FU, taxanes, or irinotecan-based chemotherapy, would seem to be as effective and tolerable as traditional platinum-based chemotherapy. Accordingly, these newer agents should be considered as a preferred option for first-line chemotherapy in the case of AGC, especially for patients where platinum-based chemotherapy is contraindicated. Furthermore, additional trials are needed to define the benefits of these agents in patients with AGC.

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