

Chemotherapy beyond second-line in advanced gastric cancer

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further lines of chemotherapy will result in substantial prolongation of survival. Despite this, the practice of offering chemotherapy beyond second-line agents to AGC patients is not uncommon if their performance status is well-preserved and they are willing to receive subsequent active treatments. The choice of chemotherapeutic agents depends on the patient's prior regimens. However, there are important controversial issues in the salvage setting of AGC, including a subset of patients who may benefit from chemotherapy, that still remain unanswered. This report reviews the available evidence regarding the impact of third- and subsequent lines of chemotherapy on survival and quality of life in patients with AGC.

Key words: Chemotherapy; Gastric cancer; Salvage

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Core tip: There no evidence to date that chemotherapy beyond second-line has a beneficial effect in patients with gastric cancer. The impact of third- and subsequent lines of chemotherapy on survival and quality of life is the subject of this review.

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Abstract

Patients with advanced gastric cancer (AGC) can be treated with multiple lines of chemotherapy. Although several randomized trials have demonstrated the benefit of second-line chemotherapy compared with best supportive care, there is no evidence that

INTRODUCTION

Although fluoropyrimidines and platinum combination chemotherapy is considered standard first-line treatment in patients with advanced gastric cancer (AGC)^[1], the overall prognosis of such patients remains

Table 1 Randomized phase III trials in the second-line treatment of gastric cancer

Trials	Treatment	No. of patients	OS (mo)	HR for OS (95%CI)	Remarks
AIO ^[8]	Irinotecan	21	4.0	0.48 (0.25-0.92)	Closed early due to poor accrual
	BSC	19	2.4	<i>P</i> = 0.012	
Korean ^[9]	Docetaxel or irinotecan	133	5.3	0.657 (0.485-0.891)	No OS difference between docetaxel (5.5 mo) and irinotecan (6.5 mo)
	BSC	69	3.8	<i>P</i> = 0.007	
COUGAR-02 ^[10]	Docetaxel	84	5.2	0.67 (0.49-0.92)	Global QOL similar between arms (<i>P</i> = 0.53)
	BSC	84	3.6	<i>P</i> = 0.01	
REGARD ^[11]	Ramucirumab	238	5.2	0.776 (0.603-0.998)	
	Placebo	117	3.8	<i>P</i> = 0.047	
RAINBOW ^[12]	Ramucirumab + paclitaxel	330	9.6	0.807 (0.678-0.962)	
	Placebo + paclitaxel	335	7.4	<i>P</i> = 0.017	
WJOG 4007 ^[15]	Paclitaxel	108	9.5	1.14 (0.88-1.49)	
	Irinotecan	111	8.4	<i>P</i> = 0.24	

BSC: Best supportive care; QOL: Quality of life.

poor^[2]. Clinical trials involving novel, targeted agents have had little success as first-line treatment for AGC, with the exception of trastuzumab in patients with human epidermal growth factor receptor 2 (HER2)-positive tumors^[3]. Fortunately, in a second-line setting, we now have evidence that chemotherapy provides substantial improvement in overall survival (OS) and quality of life (QOL)^[4]. While it is common practice to offer second- or further lines of chemotherapy to AGC patients^[5], and more than a few randomized trials have shown improved OS for certain second-line regimens^[4], chemotherapy beyond second-line is associated with responses in fewer patients^[6] and has no clinically relevant or consistent effects on OS. Since patients with progressive disease usually have poor performance status, aggressive chemotherapy may not be feasible. It is also known that response rates to chemotherapy decline with each subsequent regimen. Nevertheless, many AGC patients still receive chemotherapy beyond second-line, and in some cases are treated until death occurs, since patients and physicians sometimes have difficulty with transitioning to only supportive care. Considering the grim prognosis for AGC patients with second-line failure, the value of third- and subsequent lines of chemotherapy may be better evaluated by other outcome measures, such as improvement in QOL. This article reviews the available evidence regarding the impact of third- and subsequent lines of chemotherapy on OS and QOL in patients with AGC.

SECOND-LINE THERAPY

Even before the role of second-line chemotherapy was recently described, second- or further lines of chemotherapy have been administered for AGC patients after first-line failure^[7]. Our own retrospective analysis of AGC patients who received second-line chemotherapy found a median survival of 6.7 mo^[5], with baseline hemoglobin level and performance status being independent prognostic factors. There

is a general consensus that the role of second- and subsequent lines of chemotherapy, also called “salvage” therapy, in prolonging OS in AGC patients is modest. Response rates are less than 20% and short-lived, with a median OS of 4-6 mo^[4]. The results of several phase III trials testing the role of second-line therapy in patients with AGC have been reported (Table 1)^[8-12]. In this setting, three cytotoxic chemotherapeutic agents (paclitaxel, docetaxel, and irinotecan) and one anti-vascular endothelial growth factor receptor (anti-VEGFR) antibody (ramucirumab) have shown significant reductions in the risk of death. Notably, the hazard ratios (HRs) in all of these single-agent trials were of a similar magnitude, which is indicative of the robustness of the findings, since the investigators assessed the treatments in patients of different ethnic origins^[4]. The first trial conducted by German Arbeitsgemeinschaft Internistische Onkologie (AIO) investigators included 40 patients who received either irinotecan or best supportive care (BSC)^[8], and showed significant benefit with second-line irinotecan compared with BSC alone. The second trial was conducted by the current authors^[9], in which second-line chemotherapy with either docetaxel or irinotecan was compared with BSC in 202 Korean patients. We reported a significant survival benefit with second-line chemotherapy (5.3 mo vs 3.8 mo, HR = 0.657, 95%CI: 0.485-0.891). In the third, a COUGAR-02 trial^[10], researchers from the United Kingdom reported that second-line docetaxel improved median OS compared with BSC (5.2 mo vs 3.6 mo, HR = 0.67, 95%CI: 0.49-0.92). The trial included QOL as one of the objectives and reported similar global health-related QOL scores between the chemotherapy and BSC arms.

Despite the failure of more than a few clinical trials involving targeted agents^[13,14], two phase III trials of ramucirumab^[11,12], either as monotherapy or in combination with paclitaxel, were successful. In the REGARD trial, pretreated AGC patients were randomly assigned to receive ramucirumab or a placebo as

second-line treatment. Surprisingly, the survival benefit achieved with ramucirumab (5.2 mo vs 3.8 mo, HR = 0.776, 95%CI: 0.603-0.998) was similar to that seen in phase III trials. In the RAINBOW trial^[12], a more clinically relevant trial that is the largest to date, the addition of ramucirumab to paclitaxel was compared to paclitaxel alone for second-line therapy. The authors reported that OS was significantly longer in the ramucirumab plus paclitaxel arm than in the paclitaxel monotherapy arm (9.6 mo vs 7.4 mo, HR = 0.807, 95%CI: 0.678-0.962).

However, which regimen should be the standard of care in the second-line setting still remains unclear. For patients who failed fluoropyrimidine and platinum, paclitaxel^[12,15], docetaxel^[9,10], and irinotecan^[9,15] have all been evaluated extensively in clinical trials. Combination chemotherapy may achieve higher response rates than monotherapy, but the survival outcomes are the same^[16]. In our own retrospective analysis performed in 1455 AGC patients^[5], there was no relevant difference in median OS between patients who were treated with second-line combination and monotherapy. In addition, to achieve palliative goals with second-line chemotherapy, patients are more likely to tolerate single agents than combination therapy. Hironaka *et al.*^[15] reported the results of a phase III trial comparing irinotecan with paclitaxel in the second-line setting, and found that OS was not significantly different (9.5 mo in paclitaxel arm vs 8.4 mo in irinotecan arm, HR = 1.13, 95%CI: 0.86-1.49). Clearly, medically fit patients who failed or were refractory to first-line chemotherapy should receive second-line chemotherapy, with BSC reserved for those with a poor performance status. It should be noted that AGC is a heterogeneous disease, with substantial differences in its aggressiveness and responsiveness to therapy. The clinical outcome and prognosis in individual patients do not always conform to the published data. In daily clinical practice, outside of the strict enrollment criteria of a clinical trial, many AGC patients develop peritoneal carcinomatosis during the course of their disease^[5], leading to rapid symptomatic deterioration and chemotherapy intolerance.

THIRD-LINE THERAPY

It seems clear that, for the majority of patients, the benefit of chemotherapy beyond second-line for advanced disease is minimal to modest. However, as described above, some AGC patients still are candidates for third- or subsequent lines of therapy, despite not having an established third-line regimen to offer. More than two-thirds of patients enrolled in the Japanese second-line chemotherapy trial were treated with third-line therapy^[15]. In our own Korean phase III trial^[9], 27% of patients had received study treatment as third-line therapy, with the survival benefit of chemotherapy being preserved (HR = 0.812, 95%CI: 0.450-1.464). Nevertheless, data from these

phase III trials should be interpreted carefully because of the potential selection bias; only a small percentage of patients continue to have good performance status after second-line therapy and they are still medically fit to be offered further therapy.

CYTOTOXIC CHEMOTHERAPY

The data on third-line chemotherapy are not conclusive, since published studies have included only a small number of patients within different patient subsets. The majority of published studies have been small phase II or retrospective studies that have evaluated the feasibility of monotherapy or combinations of several cytotoxic agents. Because most AGC patients are initially treated with fluoropyrimidines and platinum^[17], it is not a good idea to include these drugs in a salvage regimen for these patients. In the third-line setting, based on the lack of cross-resistance between taxanes and irinotecan, these chemotherapeutic agents are still plausible salvage treatment options^[18]. Due to the risk of severe myelosuppression that is associated with the administration of paclitaxel or docetaxel every 3 wks, taxane monotherapy was commonly used as a weekly regimen for patients with heavily-treated disease. In small phase II studies involving paclitaxel^[19] or docetaxel^[18,20], response rates were in the range of 15%-23%, with a median OS of 4-7 mo. Irinotecan is another commonly-used chemotherapeutic agent in AGC, with a similar single-agent efficacy to taxanes^[9]. However, we should keep in mind that response rates and progression-free survival (PFS) do not always translate into a survival benefit. The choice of a third-line regimen should depend on previous treatments and, needless to say, on the patient's general condition. It is possible that the OS achieved in AGC was strongly associated with patient access to the three active chemotherapy regimens during the whole treatment course (*i.e.*, fluoropyrimidine/platinum-based first line, and second- and third-line chemotherapy with taxanes and irinotecan), which is similar to a model developed in patients with colorectal cancer^[21].

NOVEL TARGETED THERAPY

When we consider the decline in patients' performance status and tolerability to cytotoxic chemotherapy, especially after failure of second-line therapy, more effective but less toxic treatment options are needed to provide an OS benefit for patients with AGC. In the first-line setting, the HER2-directed monoclonal antibody trastuzumab was shown to be effective in HER2-positive AGC^[3]. However, trials involving another HER2 inhibitor, lapatinib, failed to show an OS benefit in the second-line setting^[14].

Targeting angiogenesis *via* the inhibition of VEGFR has been another promising strategy in AGC. Although the Avastin in Gastric Cancer (AVAGAST) trial failed to

show a significant OS benefit (12.1 mo vs 10.1 mo, HR = 0.87, 95%CI: 0.73-1.03)^[22], adding bevacizumab to first-line capecitabine and cisplatin chemotherapy was associated with increases in PFS and response rates. One may argue that this lack of correlation between the OS and PFS may be due to the lack of statistical power necessary to detect modest survival gain. We now have more optimistic results from the REGARD^[11] and RAINBOW^[12] trials involving ramucirumab in the second-line setting of AGC, as described above.

Similarly, small molecule inhibitors targeting VEGFR have been investigated in patients with AGC. However, the efficacy seen in phase II studies with sunitinib as a potential second-line treatment for AGC patients has been modest^[23,24]. We reported a prospective randomized trial comparing second-line docetaxel monotherapy with docetaxel plus sunitinib^[24], in which the addition of sunitinib to docetaxel did not prolong PFS. One of the most promising VEGFR inhibitors at present is apatinib. A randomized, placebo-controlled phase II trial conducted by Chinese investigators showed that apatinib improved PFS and OS in heavily-treated AGC patients^[25]. Of note, 43% of patients given apatinib as third-line therapy achieved disease control, which justified further testing in a phase III trial.

At the Annual Meeting of the American Society of Clinical Oncology (ASCO) in June 2014, Qin *et al.*^[26] presented a randomized phase III trial comparing apatinib with a placebo in 273 AGC patients with prior failure to second-line chemotherapy. The primary endpoint was OS and the secondary endpoints were response rate, PFS, safety, and QOL. The apatinib arm had superior PFS (78 d vs 53 d, HR = 0.44, 95%CI: 0.33-0.61), response rate (3% vs 0%), and median OS (195 d vs 140 d, HR = 0.71, 95%CI: 0.54-0.94) compared to placebo, with a manageable safety profile. Patients receiving apatinib had a higher incidence of neutropenia and thrombocytopenia, as well as proteinuria and hypertension. Additionally, severe (grade 3 or 4) hand-foot syndrome occurred in 8.5% of patients in the apatinib arm. As differences regarding QOL were not included in the presentation, full publication of this study will be of interest.

SELECTION OF PATIENTS

Since patients' QOL and performance status would diminish with advanced lines of chemotherapy, the expected OS benefit, if any, is the single most important factor in choosing a salvage regimen for AGC. To the best of our knowledge, no prospective analyses have been performed to examine prognostic and/or predictive factors in the third-line setting. Nevertheless, it is known that some patient and tumor factors are particularly helpful in selecting patients who may benefit from salvage therapy, and should be evaluated carefully. Among the clinical and laboratory factors, the most important are the

patient's performance status, some hematological and laboratory values (including hemoglobin level or serum albumin), the number of previous lines of therapy and the response obtained, and the number and site of metastases^[5,27]. In our retrospective study^[5], for patients who received supportive care only in a salvage setting, the reasons for such a decision included poor performance status (71%) and the patient's refusal (29%). Known tumor characteristics that directly influence the aggressiveness of the disease, such as peritoneal carcinomatosis, tumor grade, and Lauren classification, are also helpful. In addition, research is under way to define specific predictive factors of responsiveness to certain types of therapy. The Cancer Genome Atlas (TCGA) research network, for example, reported a comprehensive molecular evaluation of 295 gastric adenocarcinomas^[28] and proposed four distinct molecular subtypes: (1) tumors positive for Epstein-Barr virus; (2) microsatellite unstable tumors; (3) genomically stable tumors; and (4) tumors with chromosomal instability. Experience with other types of cancer has taught us that a substantial improvement in the treatment of AGC could be achieved with individualized therapy strategies^[29], including the identification of genetic alterations and the study of the molecular biology of therapeutic agents.

CONCLUSION

Although the current evidence is lacking concerning potential beneficial effects associated with administering third- or subsequent lines of chemotherapy, it is common practice to offer further chemotherapy for AGC patients after second-line failure^[5]. In this setting, no chemotherapeutic agents or regimens have a proven survival benefit over supportive care only, and thus no standard salvage therapy exists. Although taxanes and irinotecan have shown efficacy in this setting, no randomized trials have been conducted, and these regimens have low response rates. Recently, a phase III trial conducted in China demonstrated a benefit with apatinib in this setting^[26], which is a novel, orally-administered VEGFR inhibitor. It is therefore very important to emphasize that all treatment decisions must be individualized; targeting the specific histological and biological features that make a tumor unique, and the clinical features that make a patient unique.

Evidence showing an OS benefit of therapy in third- or subsequent lines of chemotherapy in patients with AGC suggests that salvage therapy may indeed become the standard of care. Administration of an active and tolerable therapy regimen may have a beneficial effect on patients' QOL, as a direct result of improvements in clinical outcome. However, these studies are few in number and await further confirmation. Based on these considerations, giving a patient the opportunity to actively participate in the selection of treatment seems to be an important factor for patient satisfaction and improved QOL. Even in

heavily-treated AGC patients, salvage therapy may be of value in terms of QOL^[30]. Furthermore, patient preference for treatment is increasingly important in clinical decision-making, and has been the subject of medical research^[31,32]. We should acknowledge that while curative treatment is not currently available, different treatment strategies, including no active therapy, may be appropriate. Accordingly, we must be willing to take the time to accurately and extensively discuss all treatment options in order to select the best treatment for each particular patient.

In summary, the role of therapy beyond second-line in AGC has not yet been established. Despite recent advances, the prognosis of AGC patients remains poor. However, we have considerable indirect evidence from a number of phase II or retrospective studies suggesting improved response rates and prolonged PFS through the use of third- or subsequent lines of chemotherapy. One may consider currently available chemotherapy regimens (*i.e.*, fluoropyrimidine plus platinum, taxanes, and irinotecan) for use during the whole treatment course, similar to that described for colorectal cancer^[21], in which three active drugs (fluoropyrimidines, oxaliplatin, and irinotecan) should all be used. Recently, a prospective phase III trial performed in Chinese AGC patients reported a survival benefit with the use of a novel, oral-targeted agent, apatinib. It is conceivable that integration of targeted agents, including ramucirumab and/or apatinib, into the treatment regimen could improve treatment efficacy in patients with AGC. While there is still controversy over the benefit of salvage therapy in the third-line setting and beyond, there should be certain patients who would derive the most benefit from the therapy. Our clinical expertise, better understanding of gastric carcinogenesis, and molecular characterization of this cancer will provide hope for more successful treatment in the future.

REFERENCES

- 1 **Wagner AD**, Grothe W, Haerting J, Kleber G, Grothey A, Fleig WE. Chemotherapy in advanced gastric cancer: a systematic review and meta-analysis based on aggregate data. *J Clin Oncol* 2006; **24**: 2903-2909 [PMID: 16782930]
- 2 **Van Cutsem E**, Haller D, Ohtsu A. The role of chemotherapy in the current treatment of gastric cancer. *Gastric Cancer* 2002; **5** Suppl 1: 17-22 [PMID: 12772882]
- 3 **Bang YJ**, Van Cutsem E, Feyereislova A, Chung HC, Shen L, Sawaki A, Lordick F, Ohtsu A, Omuro Y, Satoh T, Aprile G, Kulikov E, Hill J, Lehle M, Rüschoff J, Kang YK. Trastuzumab in combination with chemotherapy versus chemotherapy alone for treatment of HER2-positive advanced gastric or gastro-oesophageal junction cancer (ToGA): a phase 3, open-label, randomised controlled trial. *Lancet* 2010; **376**: 687-697 [PMID: 20728210 DOI: 10.1016/S0140-6736(10)61121-X]
- 4 **Park SH**. Second-line chemotherapy for patients with oesophagogastric adenocarcinoma. *Lancet Oncol* 2014; **15**: 8-10 [PMID: 24332239 DOI: 10.1016/S1470-2045(13)70580-1]
- 5 **Ji SH**, Lim do H, Yi SY, Kim HS, Jun HJ, Kim KH, Chang MH, Park MJ, Uhm JE, Lee J, Park SH, Park JO, Park YS, Lim HY, Kang WK. A retrospective analysis of second-line chemotherapy in patients with advanced gastric cancer. *BMC Cancer* 2009; **9**: 110 [PMID: 19358705]
- 6 **Hawkes E**, Okines AF, Papamichael D, Rao S, Ashley S, Charalambous H, Koukouma A, Chau I, Cunningham D. Docetaxel and irinotecan as second-line therapy for advanced oesophagogastric cancer. *Eur J Cancer* 2011; **47**: 1146-1151 [PMID: 21269822 DOI: 10.1016/j.ejca.2010.12.021]
- 7 **Wilson D**, Hiller L, Gehl JI. Review of second-line chemotherapy for advanced gastric adenocarcinoma. *Clin Oncol (R Coll Radiol)* 2005; **17**: 81-90 [PMID: 15830569]
- 8 **Thuss-Patience PC**, Kretzschmar A, Bichev D, Deist T, Hinke A, Breithaupt K, Dogan Y, Gebauer B, Schumacher G, Reichardt P. Survival advantage for irinotecan versus best supportive care as second-line chemotherapy in gastric cancer--a randomised phase III study of the Arbeitsgemeinschaft Internistische Onkologie (AIO). *Eur J Cancer* 2011; **47**: 2306-2314 [PMID: 21742485 DOI: 10.1016/j.ejca.2011.06.002]
- 9 **Kang JH**, Lee SI, Lim do H, Park KW, Oh SY, Kwon HC, Hwang IG, Lee SC, Nam E, Shin DB, Lee J, Park JO, Park YS, Lim HY, Kang WK, Park SH. Salvage chemotherapy for pretreated gastric cancer: a randomized phase III trial comparing chemotherapy plus best supportive care with best supportive care alone. *J Clin Oncol* 2012; **30**: 1513-1518 [PMID: 22412140 DOI: 10.1200/JCO.2011.39.4585]
- 10 **Ford HE**, Marshall A, Bridgewater JA, Janowitz T, Coxon FY, Wadsley J, Mansoor W, Fyfe D, Madhusudan S, Middleton GW, Swinson D, Falk S, Chau I, Cunningham D, Kareclas P, Cook N, Blazeby JM, Dunn JA. Docetaxel versus active symptom control for refractory oesophagogastric adenocarcinoma (COUGAR-02): an open-label, phase 3 randomised controlled trial. *Lancet Oncol* 2014; **15**: 78-86 [PMID: 24332238 DOI: 10.1016/S1470-2045(13)70549-7]
- 11 **Fuchs CS**, Tomasek J, Yong CJ, Dumitru F, Passalacqua R, Goswami C, Safran H, dos Santos LV, Aprile G, Ferry DR, Melichar B, Tehfe M, Topuzov E, Zalberg JR, Chau I, Campbell W, Sivanandan C, Pikiel J, Koshiji M, Hsu Y, Liepa AM, Gao L, Schwartz JD, Tabernero J; REGARD Trial Investigators. Ramucirumab monotherapy for previously treated advanced gastric or gastro-oesophageal junction adenocarcinoma (REGARD): an international, randomised, multicentre, placebo-controlled, phase 3 trial. *Lancet* 2014; **383**: 31-39 [PMID: 24094768 DOI: 10.1016/S0140-6736(13)61719-5]
- 12 **Wilke H**, Muro K, Van Cutsem E, Oh SC, Bodoky G, Shimada Y, Hironaka S, Sugimoto N, Lipatov O, Kim TY, Cunningham D, Rougier P, Komatsu Y, Ajani J, Emig M, Carlesi R, Ferry D, Chandrawansa K, Schwartz JD, Ohtsu A; RAINBOW Study Group. Ramucirumab plus paclitaxel versus placebo plus paclitaxel in patients with previously treated advanced gastric or gastro-oesophageal junction adenocarcinoma (RAINBOW): a double-blind, randomised phase 3 trial. *Lancet Oncol* 2014; **15**: 1224-1235 [PMID: 25240821 DOI: 10.1016/S1470-2045(14)70420-6]
- 13 **Ohtsu A**, Ajani JA, Bai YX, Bang YJ, Chung HC, Pan HM, Sahmoud T, Shen L, Yeh KH, Chin K, Muro K, Kim YH, Ferry D, Tebbutt NC, Al-Batran SE, Smith H, Costantini C, Rizvi S, Leibold D, Van Cutsem E. Everolimus for previously treated advanced gastric cancer: results of the randomized, double-blind, phase III GRANITE-1 study. *J Clin Oncol* 2013; **31**: 3935-3943 [PMID: 24043745 DOI: 10.1200/JCO.2012.48.3552]
- 14 **Satoh T**, Xu RH, Chung HC, Sun GP, Doi T, Xu JM, Tsuji A, Omuro Y, Li J, Wang JW, Miwa H, Qin SK, Chung IJ, Yeh KH, Feng JF, Mukaiyama A, Kobayashi M, Ohtsu A, Bang YJ. Lapatinib plus paclitaxel versus paclitaxel alone in the second-line treatment of HER2-amplified advanced gastric cancer in Asian populations: TyTAN--a randomized, phase III study. *J Clin Oncol* 2014; **32**: 2039-2049 [PMID: 24868024 DOI: 10.1200/JCO.2013.53.6136]
- 15 **Hironaka S**, Ueda S, Yasui H, Nishina T, Tsuda M, Tsumura T, Sugimoto N, Shimodaira H, Tokunaga S, Moriawaki T, Esaki T, Nagase M, Fujitani K, Yamaguchi K, Ura T, Hamamoto Y, Morita S, Okamoto I, Boku N, Hyodo I. Randomized, open-label, phase III study comparing irinotecan with paclitaxel in patients with advanced gastric cancer without severe peritoneal metastasis after failure of prior combination chemotherapy using fluoropyrimidine

- plus platinum: WJOG 4007 trial. *J Clin Oncol* 2013; **31**: 4438-4444 [PMID: 24190112 DOI: 10.1200/JCO.2012.48.5805]
- 16 **Higuchi K**, Tanabe S, Shimada K, Hosaka H, Sasaki E, Nakayama N, Takeda Y, Moriwaki T, Amagai K, Sekikawa T, Sakuyama T, Kanda T, Sasaki T, Azuma M, Takahashi F, Takeuchi M, Koizumi W; Tokyo Cooperative Oncology Group TJ. Biweekly irinotecan plus cisplatin versus irinotecan alone as second-line treatment for advanced gastric cancer: a randomised phase III trial (TCOG GI-0801/BIRIP trial). *Eur J Cancer* 2014; **50**: 1437-1445 [PMID: 24560487 DOI: 10.1016/j.ejca.2014.01.020]
 - 17 **Lim do H**, Park SH, Park KW, Kang JH, Oh SY, Hwang IG, Kwon JM, Lee SC, Lee HY, Kim HS, Lim HY, Kang WK. Retrospective analyses of cisplatin-based doublet combination chemotherapy in patients with advanced gastric cancer. *BMC Cancer* 2010; **10**: 583 [PMID: 20977739 DOI: 10.1186/1471-2407-10-583]
 - 18 **Lee MJ**, Hwang IG, Jang JS, Choi JH, Park BB, Chang MH, Kim ST, Park SH, Kang MH, Kang JH. Outcomes of third-line docetaxel-based chemotherapy in advanced gastric cancer who failed previous oxaliplatin-based and irinotecan-based chemotherapies. *Cancer Res Treat* 2012; **44**: 235-241 [PMID: 23341787 DOI: 10.4143/crt.2012.44.4.235]
 - 19 **Shimoyama R**, Yasui H, Boku N, Onozawa Y, Hironaka S, Fukutomi A, Yamazaki K, Taku K, Kojima T, Machida N, Todaka A, Tomita H, Sakamoto T, Tsushima T. Weekly paclitaxel for heavily treated advanced or recurrent gastric cancer refractory to fluorouracil, irinotecan, and cisplatin. *Gastric Cancer* 2009; **12**: 206-211 [PMID: 20047125 DOI: 10.1007/s10120-009-0524-9]
 - 20 **Lee JH**, Kim SH, Oh SY, Lee S, Lee H, Lee HJ, Kim HJ. Third-line docetaxel chemotherapy for recurrent and metastatic gastric cancer. *Korean J Intern Med* 2013; **28**: 314-321 [PMID: 23682225 DOI: 10.3904/kjim.2013.28.3.314]
 - 21 **Grothey A**, Sargent D. Overall survival of patients with advanced colorectal cancer correlates with availability of fluorouracil, irinotecan, and oxaliplatin regardless of whether doublet or single-agent therapy is used first line. *J Clin Oncol* 2005; **23**: 9441-9442 [PMID: 16361649 DOI: 10.1200/JCO.2005.04.4792]
 - 22 **Ohtsu A**, Shah MA, Van Cutsem E, Rha SY, Sawaki A, Park SR, Lim HY, Yamada Y, Wu J, Langer B, Starnawski M, Kang YK. Bevacizumab in combination with chemotherapy as first-line therapy in advanced gastric cancer: a randomized, double-blind, placebo-controlled phase III study. *J Clin Oncol* 2011; **29**: 3968-3976 [PMID: 21844504 DOI: 10.1200/JCO.2011.36.2236]
 - 23 **Bang YJ**, Kang YK, Kang WK, Boku N, Chung HC, Chen JS, Doi T, Sun Y, Shen L, Qin S, Ng WT, Tursi JM, Lechuga MJ, Lu DR, Ruiz-Garcia A, Sobrero A. Phase II study of sunitinib as second-line treatment for advanced gastric cancer. *Invest New Drugs* 2011; **29**: 1449-1458 [PMID: 20461441 DOI: 10.1007/s10637-010-9438-y]
 - 24 **Yi JH**, Lee J, Lee J, Park SH, Park JO, Yim DS, Park YS, Lim HY, Kang WK. Randomised phase II trial of docetaxel and sunitinib in patients with metastatic gastric cancer who were previously treated with fluoropyrimidine and platinum. *Br J Cancer* 2012; **106**: 1469-1474 [PMID: 22460270 DOI: 10.1038/bjc.2012.100]
 - 25 **Li J**, Qin S, Xu J, Guo W, Xiong J, Bai Y, Sun G, Yang Y, Wang L, Xu N, Cheng Y, Wang Z, Zheng L, Tao M, Zhu X, Ji D, Liu X, Yu H. Apatinib for chemotherapy-refractory advanced metastatic gastric cancer: results from a randomized, placebo-controlled, parallel-arm, phase II trial. *J Clin Oncol* 2013; **31**: 3219-3225 [PMID: 23918952 DOI: 10.1200/JCO.2013.48.8585]
 - 26 **Qin S**, Li J, Xu J, Xiong J, Wu C, Bai Y, Liu W, Tong J, Liu Y, Xu R, Wang Z, Wang Q, Ouyang X, Yang Y, Ba Y. Phase III study of apatinib in advanced gastric cancer: A randomized double-blind, placebo-controlled trial. *J Clin Oncol* 2014; **32** suppl: abstr 4003
 - 27 **Yang DH**, Bae WK, Hwang J, Yoon J, Chung I, Shim H. Prognostic factor analysis of third-line chemotherapy in patients with advanced gastric cancer. *J Clin Oncol* 2011; **29** suppl: abstr e14613
 - 28 **The Cancer Genome Atlas Research Network**. Comprehensive molecular characterization of gastric adenocarcinoma. *Nature* 2014; **513**: 202-209 [PMID: 25079317]
 - 29 **Lee J**, Ou SH. Towards the goal of personalized medicine in gastric cancer--time to move beyond HER2 inhibition. Part II: Targeting gene mutations and gene amplifications and the angiogenesis pathway. *Discov Med* 2013; **16**: 7-14 [PMID: 23911227]
 - 30 **Park SH**, Lee WK, Chung M, Bang SM, Cho EK, Lee JH, Shin DB. Quality of life in patients with advanced gastric cancer treated with second-line chemotherapy. *Cancer Chemother Pharmacol* 2006; **57**: 289-294 [PMID: 16010588]
 - 31 **Lee SJ**, Park LC, Lee J, Kim S, Choi MK, Hong JY, Park S, Maeng CH, Chang W, Kim YS, Park SH, Park JO, Lim HY, Kang WK, Park YS. Unique perception of clinical trials by Korean cancer patients. *BMC Cancer* 2012; **12**: 594 [PMID: 23234342 DOI: 10.1186/1471-2407-12-594]
 - 32 **Lee S**, Kang JH, Lim DH, Park KW, Oh SY, Hwang IG, Lee J, Park JO, Park YS, Lim HY, Kang WK, Park SH. Combined analysis of randomized controlled trial (RCT) and patient-preference trial (PPT) evaluating second-line chemotherapy (SLC) in advanced gastric cancer (AGC). *J Clin Oncol* 2012; **30** suppl: abstr 4064

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