Second-line treatments: moving towards an opportunity to improve survival in advanced gastric cancer?

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ABSTRACT

Gastric cancer is the third leading cause of cancer-related death globally with approximately 723 000 deaths every year. Most patients present with advanced unresectable or metastatic disease, only amenable to palliative systemic treatment and a median survival uncommonly exceeding 12 months. Over the last years, the efficacy of chemotherapy combination has plateaued and the introduction of the anti-human epidermal growth factor receptor 2 trastuzumab has resulted in a limited survival gain in the upfront setting. After this positive experience, first-line treatment with new targeted therapies failed to improve the outcome of advanced gastric cancer. On the contrary, second-line options, including monochemotherapy with taxanes or irinotecan and the anti-vascular endothelial growth factor receptor 2 ramucirumab, either alone or combined with paclitaxel, opened new therapeutic rooms for an ever-increasing number of patients who maintain an acceptable performance status across multiple lines. This article provides an updated overview on the current management of advanced gastric cancer and discusses how the different treatment options available may be best combined to favourably impact the outcome of patients following the logic of a treatment strategy.

INTRODUCTION

Despite a steadily decline in its incidence and mortality over the 20th century, gastric cancer (GC) remains a global public health problem as it still ranks as the fifth most common malignancy and the third leading cause of cancer-related death worldwide.[1] Furthermore, in Western countries approximately 50% of patients presents with metastatic disease at diagnosis and 40%–60% systemically relapse after radical surgery.[2] Chemotherapy represents the standard treatment for advanced gastric cancer (AGC) based on its ability to prolong survival and improve quality of life compared with best supportive care (BSC). However, even the most effective regimens are unable to achieve a median overall survival (OS) longer than 9–11 months and a 5-year OS higher than 5%–10%.[3] In addition, the significant survival benefit conferred by the anti-human epidermal

growth factor receptor 2 (HER2) trastuzumab (14–16 months) is limited to the small subset of HER2-positive disease (15%–20%).[4] Although several first-line trials with new targeted agents have carried out over recent years, none of them added a valuable benefit.[5–12]

Since it is increasingly unlikely to improve the survival of patients by a first-line treatment only, a potential way could be to expand the lines of treatment from the first- to the second-line and beyond. Indeed, currently roughly 50% of patients progressing after first-.line maintain acceptable general conditions and are still good candidates to receive further therapies. Also, the benefit of second-line chemotherapy has been convincingly established in randomised trials,[13–15] and more recently, the anti-vascular endothelial growth factor receptor 2 (VEGFR-2) ramucirumab has shown to improve survival either as single agent over BSC[16] or combined with paclitaxel over paclitaxel alone in pretreated patients.[17]

Therefore, the challenge is becoming how to incorporate the novel treatment options available to define a concept and a practice of a 'continuum of care' aimed at improving survival and quality of life of patients with AGC (Figure 1).

First-line treatment in AGC: successes and disappointments

AGC is a heterogeneous entity that encompasses two different clinical situations: the locally advanced unresectable and the metastatic disease. Though historically coupled together within clinical trials, they may portend distinct prognosis and should require different therapeutic approaches (Figure 2). If chemotherapy is the mainstay of upfront treatment in both settings, more aggressive regimens may be of choice in patients without distant metastases since they might be deemed operable following a good

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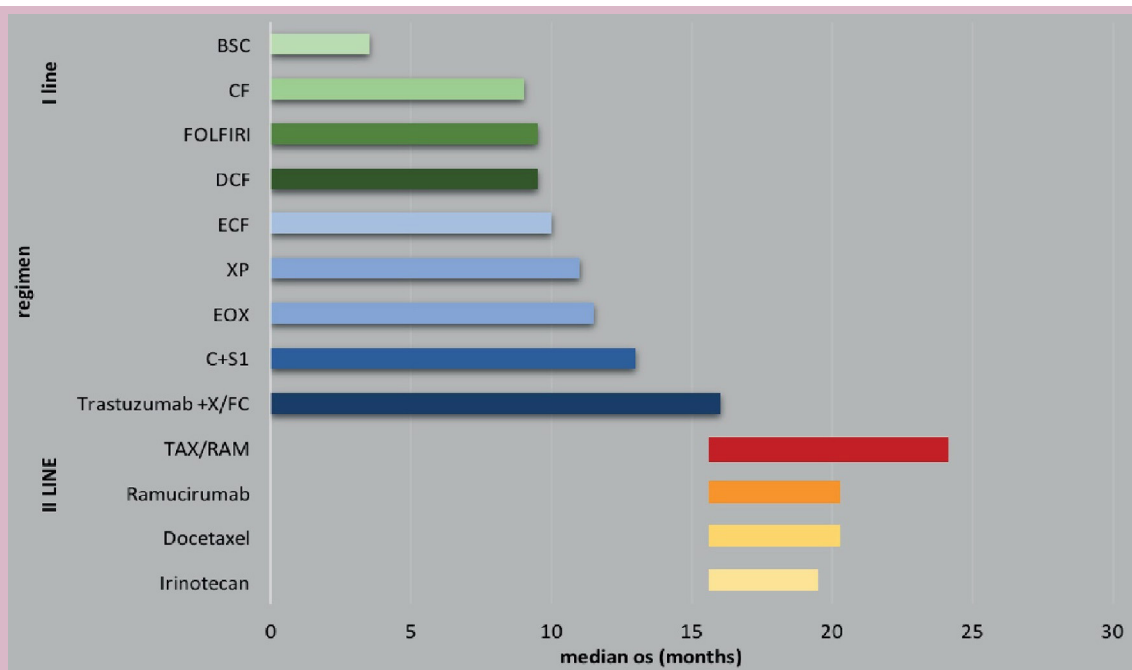Professor Stefano Cascinu;
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Figure 1 Median overall survival by chemotherapy regimen in the first- and the second-line setting for advanced gastric cancer.

response to systemic therapy, while less aggressive regimens may be more useful in patients with metastases in order to obtain palliation.

Nowadays, regimens containing platinum agents and fluoropyrimidines, with or without epirubicin or docetaxel are regarded as the standard first-line treatment. Epirubicin, cisplatin and 5-FU (ECF regimen) have become one of most adopted chemotherapy combinations, particularly in the UK.[18] Subsequently, docetaxel replaced epirubicin in the three-drug regimen.
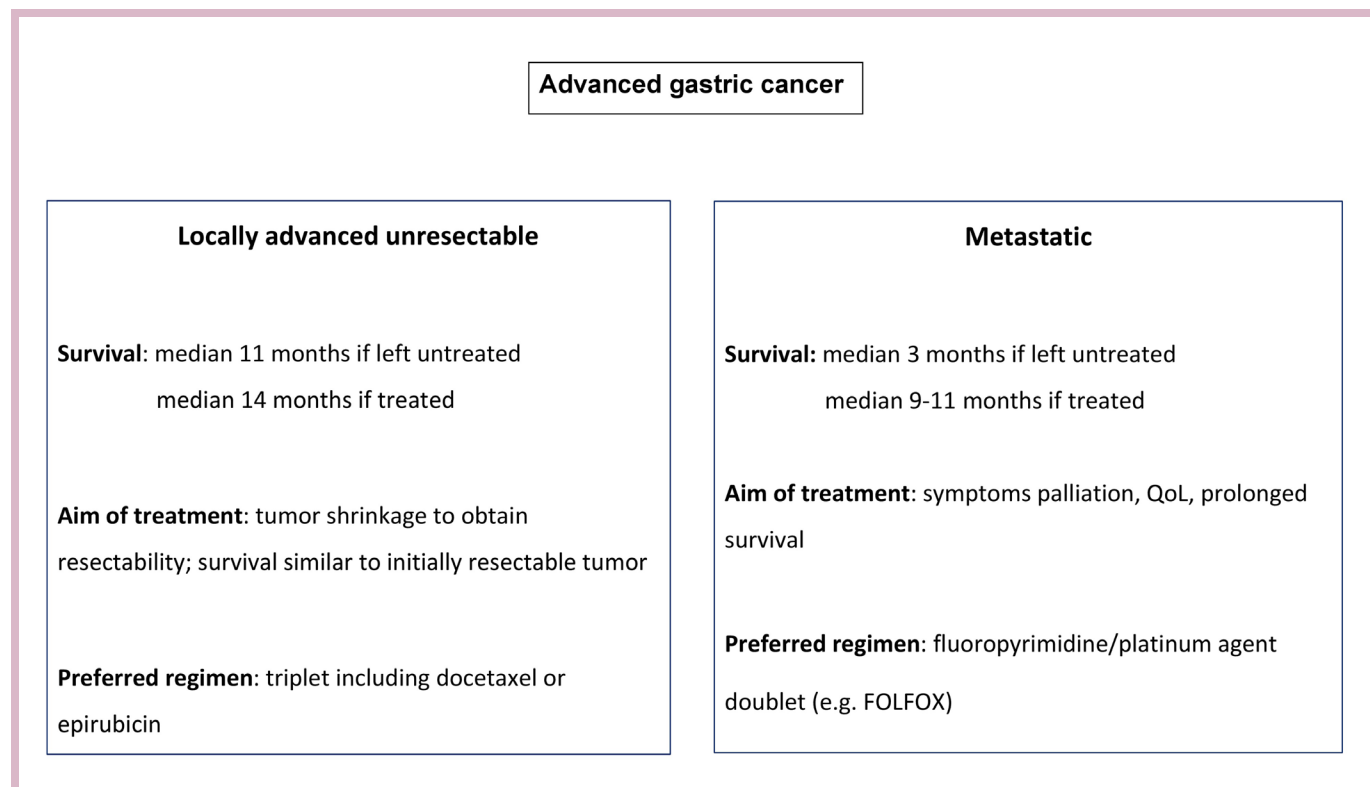

Figure 2 Advanced gastric cancer: a tale of two diseases.[68] BSC, best supportive care; ECOG, Eastern Cooperative Oncology Group.
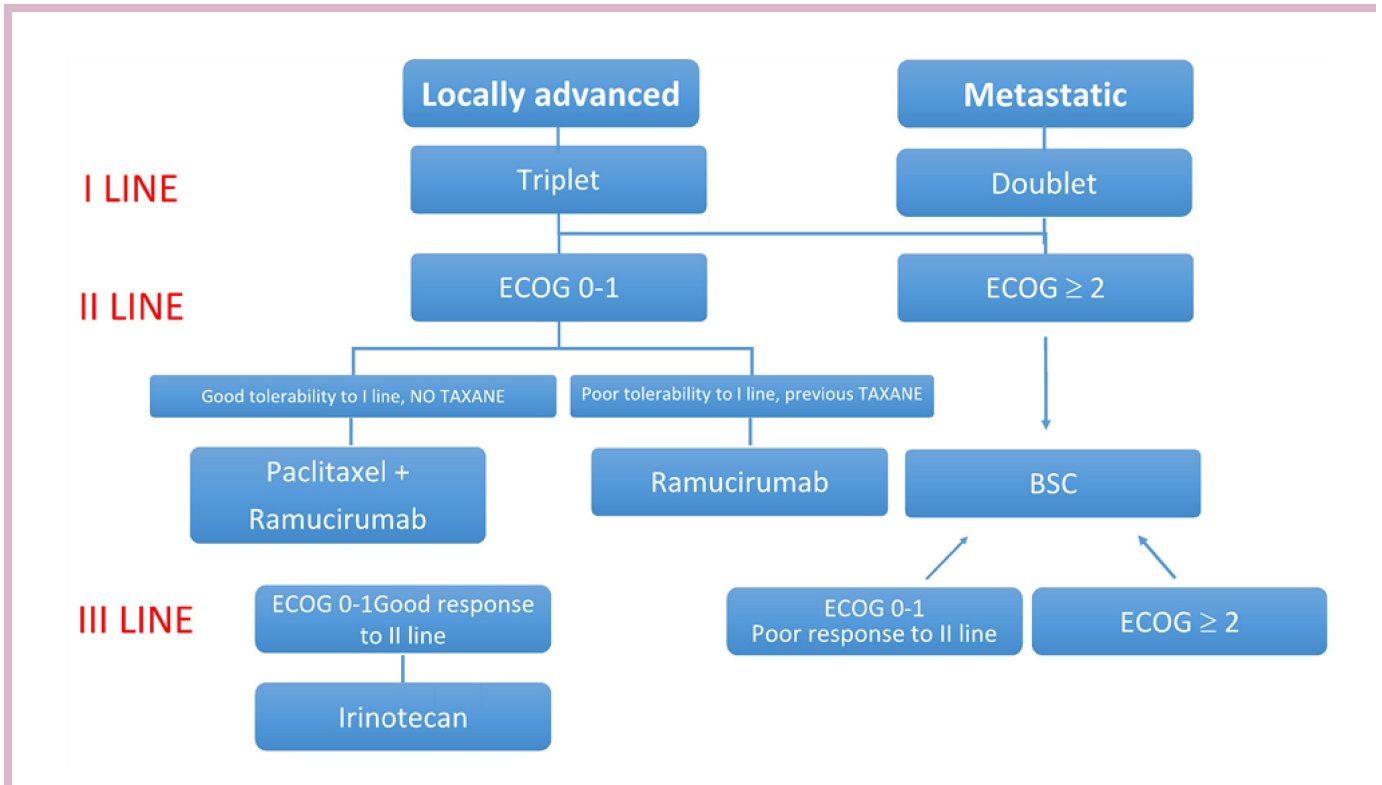
Figure 3 Algorithm for personalised allocation to treatments in patients with advanced gastric cancer. BSC, best supportive care; CF, cisplatin and 5-FU; DCF, docetaxel, cisplatin and fluorouracil; ECF, epirubicin, cisplatin and 5-FU; OS, overall survival; XP, capecitabine and cisplatin, epirubicin, oxaliplatin, and capecitabine, paclitaxel and ramucirumab.

Notably, the taxane-based regimen resulted in higher response rates (RR) but at the same time in a significantly higher incidence of grade 3–4 adverse events (AEs), with half of patients who came off study as a result.[19] Recently, Shah *et al* proposed a modified docetaxel, cisplatin and fluorouracil (DCF) regimen demonstrating a comparable efficacy and a better safety profile than parent DCF, also when supported with growth factors.[20] Nonetheless, the relevant rate of toxicity-related hospitalisation (22%) in the modified DCF arm underscores the importance to reserve taxane-based triplet for younger medically fit patients. A further development aimed at increasing tolerability without compromising efficacy was represented by the incorporation of oxaliplatin instead of cisplatin within the biweekly TEF (docetaxel, oxaliplatin, 5-FU) and FLOT regimens (5-FU, oxaliplatin, docetaxel) that showed to be active and well tolerated in the GATE and the FLOT-1 trial, respectively.[21 22]

Remarkably, the FLOT regimen has yielded higher pathological complete RR than ECF/ECX (epirubicin, cisplatin and capecitabine) (16% vs 6%; p=0.02) as perioperative therapy in resectable gastric and gastro-oesophageal adenocarcinoma.[23] These findings, while certainly expand the available options in the perioperative setting, also further strengthen the rationale for docetaxel-based triplet in the locally advanced unresectable disease.

Other contemporary trials have established the non-inferiority of oxaliplatin and capecitabine over cisplatin and 5-FU, respectively, with a more tolerable safety profile making more patients candidates to receive these combinations.[24–28] A valuable first-line alternative to platinum/fluoropyrimidine-based chemotherapy is represented by the FOLFIRI (5-FU, leucovorin, and irinotecan) combination which was shown to be at least as effective as and better tolerable than CF[29] and ECF.[30]

In Eastern countries, the novel oral fluoropyrimidine S-1 is a widely accepted standard first-line treatment option either as single agent or combined with other cytotoxics.[31–33]

Table 1 summarises key clinical trials investigating chemotherapy doublets and triplets as first-line treatment of AGC.

Finally, the discovery that approximately 20% of AGC overexpressed HER2 has prompted the development of the anti-HER2 directed therapy in this disease. In the pivotal phase III TOGA trial, 594 patients with previously untreated HER2 positive (immunohistochemistry 3+ or HER2:CEP17 ratio ≥2 on FISH) AGC were randomised to receive a chemotherapy regimen consisting of fluoropyrimidine (capecitabine or 5-FU) plus cisplatin with or without trastuzumab every 3 weeks for six cycles.[4] The overall response rate (ORR) (47% vs 35%, p=0.0017), progression free survival (PFS) (6.7

Table 1 Major randomised phase III trials of first-line chemotherapy in advanced gastric cancer.

Author (year)	Study intervention	Number of patients	Primary endpoint	ORR (%)	Median PFS/FFS/TTP (months)	Median OS (months)
Webb et al (1997)[18]	ECF vs FAMTX	274	OS	45 vs 21 (p=0.0002)	FFS 7.4 vs 3.4 (p=0.00006)	8.9 vs 5.7 (p=0.0009)
Van Cutsem et al (2006)[19]	DCF vs CF	445	TTP	37 vs 25 (p=0.01)	TTP 5.6 vs 3.7 (HR 1.47, p<0.001)	9.2 vs 8.6 (HR 1.29, p=0.02)
Cunningham et al (2008)[24]	ECF vs ECX vs EOF vs EOX	1002	OS*	40.7 vs 46.4 vs 42.4 vs 47.9 (NS)	PFS 6.2 vs 6.7 6.5 vs 7.0 (NS)	9.9 vs 9.9 vs 9.3 vs 11.2 (HR 0.80, p=0.02)†
Dank et al (2008)[29]	IF vs CF	333	TTP	31.8 vs 25.8 (NS)	TTP 5.0 vs 4.2 (NS)	9 vs 8.7 (NS)
Al-Batran et al (2008)[27]	FLO vs FLC	220	PFS	24.5 vs 34.8 (NS)	PFS 5.8 vs 3.9 (NS)	10.7 vs 8.8 (NS)
Kang et al (2009)[25]	CX vs CF	316	PFS‡	46 vs 32 (p=0.020)	PFS 5.6 vs 5.0 (HR 0.81, p<0.001)‡	10.5 vs 9.3 (HR 0.85, p<0.008)‡
Koizumi et al (2008)[31]	CS1 vs S1	305	OS	54 vs 31 (p=0.002)	PFS 6.0 vs 4.0 (HR, p<0.0001)	13 vs 11 (HR 0.77, p=0.04)
Ajani et al (2010)[33]	CS1 vs CF	1053	OS	29.1 vs 31.9 (NS)	PFS 4.8 vs 5.5 (NS)	8.6 vs 7.9 (NS)
Yamada et al (2014)[69]	OXS1 vs CS1	685	PFS, OS§	55.7 vs 52.2 (HR NR)	PFS 5.5 vs 5.4 (HR 1.004, p=0.0044)	14.1 vs 13.1 (HR 0.958, p = NR)
Guimbaud et al (2014)[30]	FOLFIRI vs ECF	416	TTF¶	39.2 vs 37.8 (NS)	TTF 5.3 vs 5.8 (NS)	9.5 vs 9.7 (NS)
Wang et al (2016)[70]	mDCF vs CF	243	PFS	48.7 vs 33.9 (p=0.0244)	PFS 7.2 vs 4.9 (HR 0.58, p=0.0008)	10.2 vs 8.5 (HR 0.71, p=0.0319)

*Noninferiority for the triplet therapies containing capecitabine as compared with fluorouracil and for those containing oxaliplatin as compared with cisplatin.
†EOX vs ECF.
‡Noninferiority of CX versus CF.
§Noninferiority in PFS for OXS1 compared with CS1; relative efficacy in OS between OXS1 and CS1.
¶TTF was significantly longer with FOLFIRI than with ECX (5.1 v 4.2 months; P = 0.008).
CF, cisplatin and fluorouracil; CS1, cisplatin and S1; CX, cisplatin and capecitabine; DCF, docetaxel, cisplatin and fluorouracil; ECF, epirubicin, cisplatin and fluorouracil; ECX, epirubicin, cisplatin, and capecitabine; EOF, epirubicin, oxaliplatin and fluorouracil; EOX, epirubicin, oxaliplatin and fluorouracil; FAMTX, fluorouracil, doxorubicin and methotrexate; FFS, failure free survival; FLC, fluorouracil, leucovorin and cisplatin; FLO, fluorouracil, leucovorin and oxaliplatin; FOLFIRI, fluorouracil, leucovorin and irinotecan; IF, irinotecan and fluorouracil; mDCF, modified docetaxel, cisplatin and fluorouracil. ORR, overall response rate; NR, not reported; NS: not significant; OS, overall survival; OXS1, oxaliplatin and S1; PFS, progression free survival; TTP, time to progression.

vs 5.5 months, p=0.0002) and OS (13.8 vs 11.1 months, p=0.0046) were all improved with the addition of trastuzumab, with the greatest benefit seen for strongly HER2-overexpressing tumours (16 vs 11.8 months, p=0.0046). The survival advantage of trastuzumab was maintained though reduced over time as shown by the decrease of HR for OS from 0.73 to 0.80 as well as the difference in median OS from 2.7 to 1.4 months on a longer follow-up.[34]

How to improve the results of first-line treatment

Regardless of the best first-line combination, more than half of patients with AGC are refractory to chemotherapy, and even in responders, disease progression invariably occurs within 6–7 months. Over the last years, the efficacy of chemotherapy seems to have achieved a plateau. Recent efforts have been made to improve patient outcomes that pointed towards two main directions: (1) addition of new biological agents to backbone chemotherapy and (2) administration of sequential lines of treatment in adequate patients.

New targeted agents

The improved knowledge of molecular underpinnings of GC has prompted the drug development process so that an unprecedented plethora of novel targeted therapeutics has been evaluated or is currently under evaluation. Epidermal growth factor receptor (EGFR), HER2, angiogenesis, MET and immune checkpoints are among the most attractive and actively investigated targets. The discovery that EGFR is overexpressed in 30%–50% of GC and associated with unfavourable prognosis[35–37] has led to two large phase III randomised trials investigating anti-EGFR monoclonal antibody in unselected patient populations. However, neither the addition of cetuximab to cisplatin/capecitabine (EXPAND trial) nor panitumumab to EOC (epirubicin, oxaliplatin, and capecitabine) regimen (REAL-3 trial) resulted in any improvement in survival.[5 6] Of note, panitumumab showed a detrimental effect on survival (OS 8.8 vs 11.3 months; p=0.013), probably due to dose reductions of the backbone cytotoxics. Among strategies to exploit HER2, lapatinib was evaluated in combination with capecitabine and oxaliplatin without showing any improvement in survival compared with chemotherapy alone in the overall HER2-amplified population. Notably, a benefit was seen in preplanned subgroup analyses of Asian and younger patients.[7] Since up to 50% of GC stain positively for MET on immunohistochemistry and 2%–10% are MET amplified, being associated with depth of tumour invasion, lymph node metastasis and poor prognosis,[38–40] several approaches have been directed against the MET/HGF axis. In the RILOMET-1 trial patients randomly assigned to the anti-HFG rilotumumab plus ECX experienced a worse survival compared with those receiving chemotherapy alone (OS 9.6 vs 11.5 months, HR 1.36; p=0.021), because of an increase in deaths in the rilotumumab arm.[8] Similarly, the enrolment onto the phase III

METGastric trial that investigated mFOLFOX6 (modified 5-FU, leucovorin, oxaliplatin) plus the anti-MET onartuzumab or placebo stopped early due to negative results from the phase II trial without showing any survival benefit.[9]

According to aforementioned results, also the targeting of angiogenesis proved unsuccessful in the first-line setting. The AVAGAST trial, which enrolled patients to receive chemotherapy with or without bevacizumab, failed to meet its primary endpoint (OS 12.1 vs 10.1 months, HR 0.87, p=0.1).[10] However, the addition of the antiangiogenics resulted in significantly improved PFS and RR, with less benefit in Asians than non-Asians. Moreover, plasma VEGF-A and neuropilin 1 emerged as potential biomarkers since patients with plasma VEGF-A levels above the median or neuropilin 1 expression below the median have been suggested to live longer, though these findings were not applicable to the subgroup of Asians and have never been validated.[41] Likewise, in the AVATAR trial which had a study design similar to that of AVAGAST, the addition of bevacizumab to capecitabine-cisplatin did not prolong OS in Chinese patients.[42]

Other antiangiogenic agents examined as first-line treatment in AGC include the anti-VEGFR-2 ramucirumab[11] and aflibercept,[12] both of which failed to improve the efficacy of the mFOLFOX regimen. The significant proportion of oesophageal cancers enrolled onto these trials has been advocated to explain the negative impact on survival of the antiangiogenic strategy. We should not consider oesophageal and gastric adenocarcinoma as they are the same disease, in fact, there are increasing data suggesting that they differ in terms of clinical features and in their genomic landscape.[43]

Notably, the RAINFALL is currently an ongoing phase III trial which further addresses the role of antiangiogenics in first line by adding ramucirumab to cisplatin/capecitabine chemotherapy (ClinicalTrials.gov Identifier: NCT02314117).

Expanding the lines of treatment: second-line chemotherapy and beyond

In the past, the lack of a robust evidence for salvage chemotherapy along with the rapid decline of patients' performance status (PS) has precluded the widespread administration of further lines of treatment. Indeed, only about 20% of patients went on to receive second-line therapy in historical studies,[44] whereas in more recent phase III trials the percentage of candidates has risen from 40% in Europe[45] to as high as 75% in Japan.[31] Recently, a growing evidence has accumulated on the effectiveness and the feasibility of second-line chemotherapy and a better delivery of cytotoxics together with the improvement in simultaneous care has allowed more patients to tolerate multiple lines of treatment.

Monochemotherapy versus BSC

Three are the landmark phase III randomised trials that successfully explored the role of second-line monochemotherapy in patients with AGC.

The German Arbeitsgemeinschaft Internistische Onkologie trial compared a 3-week schedule of irinotecan 250 mg/m² (escalated up to 350 mg/m² depending on toxicity) with BSC in patients with Eastern Cooperative Oncology Group performance status (ECOG PS) 0–2 who had received prior fluoropyrimidine/platinum combination and whose disease progressed during or within 6 months following first line.[13] Although the study was terminated prematurely due to poor accrual, among 40 enrolled patients the median OS was significantly longer in the irinotecan arm than in the BSC arm (4 vs 2.4 months, HR=0.48, p=0.023). The UK COUGAR-2 trial enrolled 168 patients to receive either docetaxel 75 mg/m² every 3 weeks plus BSC for a maximum of six cycles or BSC alone.[15] The median OS was improved with docetaxel compared with BSC (5.2 vs 3.6 months, HR=0.67, p=0.01). Despite a higher incidence of grade 3–4 neutropenia, infection and febrile neutropenia, patients receiving docetaxel experienced less pain, nausea, vomiting and constipation and decreased dysphagia and abdominal pain.

A Korean trial tried to answer the question about the optimal cytotoxics to be used in second line. In this study, 202 patients with ECOG PS 0–1 and failing one or two prior chemotherapy lines were randomised in a 2:1 ratio to either salvage chemotherapy (docetaxel 60 mg/m² every 3 weeks or irinotecan 150 mg/m² every 2 weeks upon investigator's choice) or BSC.[14] The administration of second-line chemotherapy resulted in a significant improvement in OS compared with BSC (5.3 vs 3.8 months, HR=0.657, p=0.007), while no survival difference was recorded between docetaxel and irinotecan (5.2 vs 6.5 months, p=0.116). Even side effects were similar in both treatment arms.

A meta-analysis of patient-level data from the above-mentioned trials including a total of 410 patients underscored the median OS gain of roughly 2 months for second-line monochemotherapy as compared with BSC, with a significant reduction in the risk of death by 37% (HR=0.63, p<0.0001). This benefit was conferred by both irinotecan and docetaxel and was of similar magnitude through patients of different ethnic origin.[46] Of note, when we consider these results we have to remind that the docetaxel benefit is limited to a 3-week schedule at a higher dose, while the weekly lower dose regimen did not seem to yield a similar advantage.[47]

On the contrary, a weekly paclitaxel regimen provided an OS comparable to that achieved with irinotecan in 219 patients refractory to standard first-line treatment (9.5 vs 8.4 months, HR=1.13, p=0.38).[48]

Combination chemotherapy versus monochemotherapy

Unlike the first-line setting, combination chemotherapy failed to demonstrate a survival benefit over single.-agent in pretreated AGC. In a small Korean phase II trial, irinotecan monotherapy was as effective as FOLFIRI in terms of ORR (17.2% vs 20%, p=0.525), PFS (2.2 vs 3.0 months, p=0.481) and OS (5.8 vs 6.7 months, p=0.514); grade 3–4 toxicity was also superimposable between treatment arms.[49] In another Japanese phase III study comparing biweekly irinotecan (60 mg/m²) plus cisplatin (30 mg/m²) to biweekly irinotecan alone (150 mg/m²) in 130 patients refractory to S1-based first-line chemotherapy, PFS was significantly prolonged in the combination arm (3.8 vs 2.8 months, HR 0.68, p=0.0398) but OS did not.[50] A meta-analysis of 10 randomised trials confirmed that doublet chemotherapy does not significantly improve OS compared with single agent, while resulting in more grade 3–4 myelosuppression, diarrhoea and fatigue, suggesting monochemotherapy as standard of care in this setting.[51]

Ramucirumab: single agent and combinatorial approach

In spite of negative results coming from first-line trials, the therapeutic exploitation of angiogenesis turned out to be effective in second line. Ramucirumab, a fully human immunoglobulin IgG1 monoclonal antibody targeting VEGFR-2, has been shown to significantly improve survival in two pivotal international phase III double-blind, placebo-controlled trials. In the REGARD trial, 355 patients whose disease progressed within 4 months of fluoropyrimidine or platinum-containing first-line chemotherapy or within 6 months of completion of adjuvant therapy, and with an ECOG PS of 0–1, were randomised in a 2:1 ratio to either ramucirumab 8 mg/kg or placebo, intravenously every 2 weeks.[16] Patients receiving ramucirumab had an improvement in both OS (5.2 vs 3.8 months, HR=0.776, p=0.047) and PFS (2.1 vs 1.3 months, HR=0.48, p<0.0001), with a reduction in the risk of death by 22% compared with placebo. Also, the disease control rate was significantly higher in the experimental arm (49% vs 23%), although objective responses were infrequent with ramucirumab. The survival benefit remained significant after adjusting for main prognostic variables such as PS, tumour location and peritoneal disease. The efficacy of ramucirumab alone was comparable to that reported in phase III trials of second-line chemotherapy, with a more favourable toxicity profile.

Similarly, in the RAINBOW trial, which is the largest second-line trial in AGC, the addition of ramucirumab to weekly paclitaxel significantly prolonged either median OS (9.6 vs 7.4 months, HR=0.807, p=0.017) or PFS (4.4 vs 2.9 months, HR=0.635, p<0.0001) when compared with paclitaxel monotherapy in 665 patients.[17] A decrease in the risk of death by 19% was seen and a significantly greater proportion of patients attained an objective response in the combination group than in the single-agent group (28% vs 16%, p=0.0001). These results are noteworthy especially in the light of poor risk feature of patients enrolled as demonstrated by the rate of peritoneal metastases higher than 40% in both the experimental and control arms. In a preplanned subgroup analysis, Asian patients derived less survival benefit than non-Asian. A

Table 2 Major randomised phase III trials of second-line treatments in advanced gastric cancer.

Trial	Study intervention	Number of patients	Median PFS (months)	Median OS (months)	Grade ≥3 AEs in the experimental arm
AIO[*]	Irinotecan + BSC vs BSC	40	2.6 vs NR	4.0 vs 2.4 HR 0.48, p=0.012	Diarrhoea 26%, leucopenia 21%, febrile neutropenia 16%
Kang et al[14]	Docetaxel or irinotecan vs BSC	202	NR	5.3 vs 3.8 HR 0.65, p=0.007[†]	Anaemia 31%, fatigue 18%, neutropenia 17%
WJOG 4007[48]	Paclitaxel vs irinotecan	219	3.6 vs 2.3	9.5 vs 8.4 HR 1.13, p=0.38	Neutropenia 39.1%, anaemia 30%, anorexia 17.3%
COUGAR-02[15]	Docetaxel + BSC vs BSC	168	NR	5.2 vs 3.6 HR 0.67, p=0.01	Neutropenia 15%, infection 19%, febrile neutropenia 7%
REGARD[16]	Ramucirumab + BSC vs BSC	355	2.1 vs 1.3	5.2 vs 3.8 HR 0.77, p=0.047	Hypertension 8%, fatigue 6%, abdominal pain 6%
RAINBOW[17]	Ramucirumab + paclitaxel vs paclitaxel	665	4.4 vs 2.8	9.6 vs 7.4 HR 0.87, p=0.017	Neutropenia 41%, leucopenia 17%, hypertension 14%

*Prematurely closed due to poor patients accrual.
†No OS difference between docetaxel (5.2 moths) and irinotecan (6.5 months).
AIO, Arbeitsgemeinschaft Internistische Onkologie; AE: adverse event; BSC: best supportive care; NR: not reported.

dilution effect by poststudy discontinuation treatment as well as difference in pharmacokinetics has been advocated to explain this discrepant outcome. Interestingly, the survival benefit was achieved while maintaining patient quality of life, delaying symptom worsening and functional status deterioration.[52] The toxicity of ramucirumab was tolerable and, as expected, higher in the combination regimen. In the single-agent trial the most common AE was an increased risk of grade 3 or higher hypertension (8% vs 3%), while when combined with paclitaxel, ramucirumab resulted in significantly increased rates of grade 3–4 neutropenia (40.7% vs 18.8%), though this did not translate into higher incidence of febrile neutropenia. Antiangiogenic class side effects such as proteinuria, bleeding and gastrointestinal perforations were mainly infrequent, mild in grade and more commonly noted in the combination arm.

Table 2 summarises efficacy and safety results from major randomised phase III trials investigating second-line treatments in patients with AGC.

Third-line treatment

Although currently not supported by randomised data, third-line chemotherapy is increasingly administered to patients failing previous lines and maintaining an acceptable PS, particularly in Asian countries. As such, more than 70% and 27% of patients received a third-line chemotherapy in a Japanese[48] and Korean[14] phase III trial of second-line chemotherapy, respectively. Sparse data from small phase II and retrospective studies suggested an RR in the range of 15%–23% for single-agent taxanes and irinotecan[53–55] but their impact on patients' quality of life and survival is unknown. Since patients' PS is expected to deteriorate with the advancement in lines of treatment and the absolute benefit of therapy reduced, it is mandatory to carefully select those candidates to further treatment.

It has been reported that ECOG PS, serum albumin, histological type and PFS under second line are independent prognostic factors for survival in patients receiving third-line chemotherapy, thus serving as a useful tool to guide treatment decision.[56] Lately, apatinib, a novel receptor tyrosine kinase inhibitor selectively targeting VEGFR-2, has shown to significantly prolong survival compared with placebo in Chinese patients who experienced disease progression after two or more lines of systemic therapy (6.5 vs 4.7 months, p=0.0156).[57] This is the first agent that proved effective in heavily pretreated AGC. Likewise, a very recent abstract presented by Kang and colleagues at the 2017 Gastrointestinal Cancer Symposium reported extremely promising results on the anti-PD1 nivolumab. In the phase III randomised ONO-4538-12 study, 493 patients who failed two or more previous lines of chemotherapy were randomly allocated to nivolumab 3 mg/kg every 2 weeks or placebo. Nivolumab resulted in significantly improved ORR (11.2% vs 0%), PFS (1.61 vs 1.45 months) and OS (5.32 vs 4.14 months) and lower grade ≥3 AEs (11.5% vs 5.5%) compared with placebo.[58]

The nutritional issue of patients with AGC

Malnutrition is emerging as a highly prevalent comorbid condition in patients with cancer, including GC, characterised by progressive depletion of nutritional status and worsening of metabolic alterations. While weight loss >10% of usual weight within previous 6 months was reported in 15% of GC at diagnosis, malnutrition has been described in up to 80% of AGC.[59] Factors known to deteriorate the nutritional status depend on both disease and treatment-related catabolic effects. An impaired nutritional status is associated with increased morbidity and mortality during anticancer treatment since patients who are malnourished commonly require dose reductions, delays or even treatment

discontinuation, higher frequency of hospitalisation, reduced quality of life and ultimately decreased survival. In particular, malnutrition may be responsible for increased treatment-related toxicities through sarcopenia, a low level of muscle mass, which results in higher drug exposure as demonstrated by the higher area under the time–concentration curve in patients with sarcopenia versus patients without sarcopenia.[60] Moreover, nutritional deterioration combined with energy and protein deficiencies has been suggested to have a significant impact on quality of life, even superior of cancer stage. This has been reported to occur early even before starting any oncological treatment and it is independent from oncological characteristics.[61]

There is accumulating evidence that for non-imminently dying patients with AGC nutritional support may be beneficial in terms of both quality of life and survival. When feasible, the oral and enteral routes are preferred to the parenteral one, although patients with AGC may often have an impaired gastrointestinal function depending on several factors: stenosis of the cardia or pylorus, peritoneal carcinosis, chemotherapy-related gastrointestinal side effects, short bowel syndrome, which contraindicate enteral feeding. In a study by Qiu and colleagues, the nutritional support has shown to improve the prognosis of high nutritional risk AGC (nutritional risk score ≥3), which obtained an NRS shift to <3 (median survival 14.3 vs 9.6 months, p=0.001).[62] Similarly, short-term home parental nutrition is largely indicated based on the improved quality of life, and nutritional and functional status seen in patients who are malnourished and with AGC; however, this did not affect neither the toxicity nor the RR of treatment.[59]

Given the high prevalence and early onset of malnutrition, nutritional screening and assessment should become an integral part of care in AGC in order to establish an adequate and prompt intervention to maintain or even improve patients' outcomes and quality of life.

DISCUSSION

Akin to colorectal cancer, it seems that the management of AGC is witnessing a shift from a step-by-step approach to a tailored therapeutic strategy in which oncologists can plan to give the patients sequentially over the entire disease course all active agents available in order to improve their outcome. In this scenario, the challenge becomes how to best integrate and combine emerging therapies into a treatment paradigm that started looking beyond first line along a continuum of care. The pivotal driver of this decision-making process is the goal of treatment, which ranges from symptoms palliation and prolongation of survival for the vast majority of patients to rarely cure. Moreover, given the paucity of validated predictive and prognostic factors, the choice of the optimal treatment strategy should involve clinical factors pertaining to both the patient and the disease. Based on data from clinical trials and on the different treatment aims, we propose an

algorithm as guidance for the management of patients with AGC (Figure 1).

As such, the higher RR yielded by taxane-containing triplets (ORR 37%–48%) makes them reasonable upfront treatment options for locally advanced unresectable GC to maximise the chance of resectability and ultimately cure, since salvage surgery is the single most important predictor of survival after neoadjuvant chemotherapy.[63] Similarly, three-drug regimens may be offered to selected suitably fit patients suffering from tumour-related symptoms and/or bulky disease who therefore require rapid shrinkage. Current available literature suggests similar activity for epirubicin and docetaxel-based regimens in AGC but different safety profiles, with a decrease in the risk of diarrhoea, stomatitis, neutropenia and fatigue for the former and a decrease in the risk of thrombocytopenia, anaemia, nausea, vomiting, and hand and foot syndrome for the latter.[64]

On a different approach, for metastatic disease and for patients deemed unfit for triplets, the combination of a fluoropyrimidine and a platinum agent should represent the preferred backbone of first-line treatment palliation in HER2 negative AGC. Particularly, the mFOLFOX regimen is advocated over cisplatin-containing doublets based on its greater efficacy and safety.[65 66] Second-line treatment has unquestionably become a standard of care for several patients with AGC. In this view, the adequate selection is a crucial step able to identify patients more likely to benefit from a treatment beyond first line while sparing them unacceptable toxicities. Several clinical factors have been associated with outcome in patients who receive second-line therapy. Catalano and colleagues found ECOG PS>2, haemoglobin ≤11.5 g/L, CEA>50 ng/mL, three more metastatic sites and time to progression on first line ≤6 months as independent predictors of poor survival in multivariate analysis.[45] Accordingly, a more recent study based on individual data of 868 patients suggested that those with favourable ECOG PS (0–1), lower LDH level (≤480 U/L), lower neutrophils/lymphocytes ratio (2.7) and longer PFS in first line (≥6.8 months) achieve better outcomes.[67] According to this, patients who maintain a good PS (0–1) and have a longer time to progression after first line are the optimal candidates to second-line therapy. For those receiving a taxane-free regimen (either a doublet or a triplet) in the upfront setting, the combination of ramucirumab and paclitaxel should be the preferred choice. Contrariwise, patients not amenable to the combination owing to poor tolerability to first line, residual toxicity or personal preference could receive single-agent ramucirumab. Other valuable options in adequate patients are taxanes or irinotecan monotherapy, which have similar activity but increased toxicity compared with the anti-VEGFR-2 alone and a lower activity and an equivalent toxicity in comparison with paclitaxel/ramucirumab combination.

Finally, the question of how to treat patients with impaired PS is still open since those with an ECOG PS of 2 or worse were under-represented in the trials

of chemotherapy (total of 37 patients) and were not included neither in the REGARD nor in the RAINBOW trial. Therefore, BSC alone should be offered to patients with poor PS (≥2) and/or unwilling for further treatment.

Search strategy and selection criteria

A search of the literature was done on PubMed using the keywords 'advanced gastric cancer' paired with 'chemo-therapy', 'first-line', 'second-line', third-line', 'targeted agent' and 'immunotherapy'. Only articles published in English language up to 25 March 2017 were considered. Other articles were retrieved by searching manually and cross-referencing the bibliography of relevant studies.

Contributors All authors searched the data and literature. MS drafted the first version of the text. All authors wrote the text, prepared the tables and figures, and agreed to the final version of the manuscript.

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