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Influence of Taxanes on Treatment Sequence in Gastric Cancer

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Abstract
Background: Adenocarcinoma of the stomach and esophagogastric junction (EGJ) remains a tumor entity with a poor prognosis. While meaningful advances have been made in the treatment of other solid tumors in the past years, numerous phase III studies in gastric cancer have had negative outcomes. Successes of targeted therapies so far include the introduction of trastuzumab in the first-line treatment of HER2-positive gastric cancer, and second-line anti-angiogenic treatment with the anti-VEGF-2 receptor antibody ramucirumab. Taxanes have become established in the perioperative setting and in second-line treatment and have set new standards. However, evidence for improved overall survival in the first-line treatment of advanced gastric cancer with taxanes is not convincing. ***Methodology:*** Expert consensus discussion on the scientific and clinical evidence for sequential systemic treatment for advanced gastric and EGJ cancer, taking into account data clinical outcomes from randomized controlled phase II and phase III trials. ***Summary:*** In first-line treatment of advanced gastric cancer, taxanes in combination with a platinum- and 5-fluorouracil-based regimen are generally not recommended because they lack a survival benefit and confer high toxicity. However, taxanes in first-line can be a treatment option for patients presenting with high tumor burden and strong pressure to achieve remission. Since the publication of several positive studies in second- and third-line therapy, sequential therapy is playing an increasingly important role in metastatic gastric and EGJ cancer. ***Key Message:*** Standard of care for the first-line treatment of gastric cancer is a platinum-fluoropyrimidine chemotherapy doublet combination. The standard of care after failure of platinum-based first-line therapy is ramucirumab in combination with paclitaxel. Data supporting this combination after previous taxane therapy are not yet available.

Introduction

In contrast to the declining figures for gastric cancer, the incidence of esophagogastric junction (EGJ) tumors has been rising exponentially over the last decades, especially in regions with a Western lifestyle. Metastatic gastric and EGJ cancer therefore continues to be one of the most common cancer-related causes of death with a very short median survival of less than 12 months [1]. The modest number of convincing and successful studies in the treatment of gastric cancer is outweighed by a large

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Table 1. Randomized-controlled phase III studies comparing taxane-containing triplet chemotherapy versus taxane-free doublet chemotherapy for patients with advanced/metastatic gastric or EGJ cancers (FLOT65 recruited also patients with localized resectable gastric cancer)

Study [Ref.]	Patients, *n*	Triplet regimen	Doublet regimen	OS	PFS	ORR
V325 [8]	445	Docetaxel-cisplatin-5FU (DCF)	Cisplatin-5-FU	9.2 vs. 8.6 mo. HR = 1.29 $p = 0.02$	5.5 vs. 3.7 mo. HR = 1.47 $p < 0.001$	37 vs. 25% $p = 0.01$
JCOG1013 [10]	741	Docetaxel, cisplatin, S1 (DCS)	Cisplatin, S1 (CS)	14.2 vs. 15.3 mo. HR = 0.99 $p = 0.47$	7.4 vs. 6.5 mo. HR = 0.99 $p = 0.92$	59 vs. 56% $p = 0.50$

HR, hazard ratio; mo., months; *n*, number; OS, median overall survival; ORR, overall response rate; PFS, progression-free survival; TTP, time to progression.

number of negative clinical trials. We are also unfortunately seeing a number of very recent negative outcomes of phase III immunotherapy studies such as JAVELIN Gastric 300 and KEYNOTE-61 [2, 3]. Targeted treatment concepts with cetuximab and panitumumab (epidermal growth factor receptor), lapatinib, pertuzumab plus trastuzumab and trastuzumab emtansine (human epidermal growth factor receptor 2, HER2), rilotumumab and onartuzumab (mesenchymal-epithelial transition factor proto-oncogene-receptor-tyrosine kinase), amongst others, failed to demonstrate sufficient efficacy in adenocarcinomas of the stomach and EGJ.

Trastuzumab in HER2-positive gastric cancer remains one of the very few established targeted treatment options, [4]. Taxane-based treatment regimens are also used on a regular basis. Their efficacy in the perioperative treatment of gastric and EGJ tumors (FLOT = 5-fluorouracil [5-FU], leucovorin, oxaliplatin and docetaxel]), in purely neoadjuvant therapy of esophageal and EGJ tumors (CROSS = paclitaxel, carboplatin and radiotherapy) has been documented in randomized phase III trials [5–7]. However, their role in the first-line treatment for advanced gastric and EGJ tumors is not convincing. An overall survival (OS) benefit for a taxane-containing triplet (DCF, docetaxel-cisplatin-5-FU) versus a taxane-free doublet (cisplatin-5-FU) was demonstrated in an old randomized controlled phase III study (V325), in which patients had very short survival outcomes in the control arm due to lack of sequential treatment options in most patients. Moreover, treatment-related toxicity was shown to be significantly increased with a triplet versus a doublet chemotherapy combination [8]. A Cochrane-based systematic review of older studies mostly published <10 years ago indicated that docetaxel extends OS slightly (just over 1 month) compared to non-docetaxel-containing regimens (hazard ratio [HR] 0.86, 95% confidence interval 0.78–0.95, 2,001 participants, 8 studies, high-quality evidence). However, due to subgroup analyses, authors were uncertain whether docetaxel-containing combinations (docetaxel added to a single-agent or two-drug combination) extend OS due to moderate-quality evidence (HR 0.80, 95% CI 0.71–0.91, 1,466 participants, 4 studies) [9]. In contrast, a newly published phase III study (JCOG1013), which is reflecting contemporary treatment options for advanced gastric and EGJ cancers does not show any survival benefit for the integration of docetaxel into first-line treatment of advanced gastric and EGJ cancers, while treatment-related toxicity with a three-drug combination remains high [10]. Table 1 illustrates outcomes of randomized controlled phase III studies comparing taxane-based first-line triplet versus taxane-free first-line doublet chemotherapy. In elderly patients, detrimental effects of FLOT versus FLO on health-related quality of life have been demonstrated in a randomized controlled phase II study without conferring any improvement in survival-related outcomes [11]. In contrast, for second-line treatment, the combination of a taxane and anti-angiogenic drug (ramucirumab plus paclitaxel) has been established in the RAINBOW study as a standard of care in Germany, Europe and beyond [9, 12, 13]. Apart from paclitaxel-ramucirumab, several other second- and third-line therapies have shown efficacy in recent studies and can be considered as treatment options (Table 2).

Open Questions in Real-World Practice

German S3 guidelines lack specific recommendations on whether and how sequential taxane-based therapy might be usefully integrated into the treatment algorithm for these tumors [12]. The "Onkopedia" guidelines provide more differentiated advice, defining a doublet regimen without taxane as standard of care [25]. This is important to the extent that similar mechanisms of action and resistance as well as overlapping

Table 2. Randomized-controlled phase III studies comparing novel treatment options with standard therapy in second-line advanced gastric or EGJ cancer

Study	Patients, *n*	OS, months	Hazard ratio	*p* value	First author, year [Ref.]
GERMAN (AIO) Irinotecan vs. BSC	40	4.0 vs. 2.4	0.48	0.012	Thuss-Patience, 2011 [19]
KOREAN Irinotecan or docetaxel vs. BSC	202	5.3 vs. 3.8	0.657	0.007	Kang, 2012 [18]
COUGAR2 Docetaxel vs. BSC	168	5.2 vs. 3.6	0.67	0.001	Ford, 2014 [17]
WJOG 4007 Irinotecan vs. paclitaxel	219	8.4 vs. 9.5	1.13	0.38	Hironaka, 2013 [20]
REGARD Ramucirumab vs. BSC	355	5.2 vs. 3.8	0.78	0.047	Fuchs, 2014 [22]
RAINBOW Paclitaxel vs. paclitaxel + ramucirumab	665	7.4 vs. 9.6	0.81	0.017	Wilke, 2014 [21]

BSC, best supportive care; *n*, number; OS, overall survival.

toxicity profiles may restrict taxane reuse. A number of important questions arise for real-world practice, including the following:

- There are limits to administering taxane-based therapies in successive treatment lines. During treatment which taxane-based therapy should be administered in order to obtain the best possible result for the patient?
- Under which circumstances should a triplet regimen with a taxane be considered for first-line therapy?
- Does reexposure to a taxane in the metastatic setting make sense if a taxane was already administered in the perioperative or neoadjuvant setting (e.g., FLOT or CROSS)?

Methodology

A face-to-face expert discussion took place on 18 November 2018 in Berlin at the invitation of Lilly Deutschland GmbH. All randomized controlled trials and systematic reviews on systemic therapy for advanced gastric and EGJ cancer that had been fully published or presented at major meetings like European Society for Medical Oncology or American Society of Clinical Oncology within the past 25 years were searched via PubMed and the respective society-based webpages. This was done in the weeks before the meeting. The scientific and clinical evidence of these data was reviewed by each single member of the meeting and then discussed on 18 November using prespecified questions. The impact of scientific data on contemporary clinical treatment algorithms was discussed with the ultimate goal to develop pragmatic and patient outcome-oriented recommendations for the best use of first-, second-, and further-line treatment for advanced gastric and EGJ cancer, with a particular focus on the best integration of taxanes.

The following paragraph gives a brief outline of the results of the main randomized controlled studies investigating taxane-based therapies in locally advanced and metastatic gastric and EGJ cancer.

Taxanes in a Perioperative Setting

The FLOT-4 trial compared the FLOT regimen with the previous standard treatment, i.e. ECF (epirubicin, cisplatin, 5-FU) or ECX (epirubicin, cisplatin, capecitabine) in histologically confirmed clinical stage 2A or higher (cT2 or higher or nodal positive stage (cN+) or both) gastric or EGJ cancer. A higher rate of pathologic complete response was achieved using FLOT versus ECF/ECX (16 vs. 6%), and improved progression-free survival (PFS) (HR 0.75; median 30 vs. 18 months; $p = 0.004$) and OS (HR 0.77; median 50 vs. 35 months; $p = 0.012$) were reported, with comparable toxicity rates [6].

Taxanes in the First-Line Treatment of Patients with Metastatic Disease

The launch of taxanes in the first-line treatment of metastatic adenocarcinoma of the stomach and EGJ began in 2006. The V325 trial was a phase III study investigating the efficacy of docetaxel with cisplatin and 5-FU (DCF) [8, 14, 15]. The DCF combination produced a significant but very minor prolongation of OS (median 9.2 vs. 8.6 months; $p = 0.02$), time to tumor progression (median 5.6 vs. 3.7 months; $p < 0.001$), and overall response rate (ORR; 37 vs. 25%; $p = 0.01$). These benefits were as-

sociated with a major increase in toxicity. The incidence of grade 3/4 neutropenia in the DCF arm was 82% (vs. 57% with cisplatin/5-FU), and the incidence of febrile neutropenia was 29% (vs. 12%). Non-hematologic toxicity was also increased in the taxane arm: grade 3/4 diarrhea 19 versus 8% and fatigue 19 versus 14%.

Docetaxel was integrated 2 years later in an adapted protocol with 5-FU, leucovorin, and oxaliplatin (FLOT) in a non-randomized phase II study [5]. This biweekly (once every 2 weeks) protocol achieved median OS of 11.1 months, median PFS of 5.2 months and an ORR of 57.7% in first-line treatment in an uncontrolled single-arm phase II study.

The following incidences of grade 3/4 toxicities were observed in this treatment regimen: neutropenia 48.1%, neutropenia with complications (including febrile neutropenia) 3.8%, diarrhea 14.8%, fatigue 11.1%, and peripheral neuropathy 9.3%. The FLOT protocol thus showed good efficacy with a better toxicity profile than the DCF protocol. Nevertheless, the FLOT protocol demonstrated no improvement in survival outcomes compared with the taxane-free FLO protocol in older patients in a randomized phase II study but was associated with substantially higher toxicity and a significant deterioration of quality of life [11]. Another phase II trial evaluated the so-called modified DCF regimen with reduced dosage but 2 weekly applications with standard DCF. Modified DCF was better tolerable, showed a trend towards an improved PFS and had a superior OS (mOS 18.8 vs. 12.6 months) compared to standard 3-weekly DCF [24]. In a recently published phase III study, the addition of docetaxel to a platinum-fluoropyrimidine doublet regimen likewise produced no survival benefit. This study was presented as an abstract at the time of the meeting and has fully been published meanwhile [10].

Taxanes in Second-Line Therapy

About 40% of gastric and EGJ cancer patients in Europe receive 2nd-line chemotherapy after progression on first-line treatment [16]. Three randomized studies demonstrated that second-line chemotherapy prolongs OS by about 1.5 months [17–19], improves symptom control, and leads to longer maintenance of quality of life [17]. The phase III studies indicated these benefits for docetaxel and irinotecan. Paclitaxel is another effective treatment option [20].

Moreover, the introduction of the anti-angiogenic agent ramucirumab in the phase III RAINBOW study in combination with paclitaxel compared with paclitaxel alone achieved a significant increase in OS (HR 0.807; median 9.6 vs. 7.4 months; $p = 0.169$) and PFS (HR 0.635; median 4.4 vs. 2.9 months; $p < 0.001$) [21]. Overall response rate almost doubled (28 vs. 16%). The grade 3/4 toxicity rate was 41% (vs. 19%) for neutropenia. The incidence of fatigue was 12% in the combination arm (vs. 5%). At 15% (vs. 3%), the most common side effect was hypertension.

Ramucirumab on its own also produced a statistically significant improvement in OS (5.2 vs. 3.8 months) and PFS (2.1 vs. 1.3 months) versus placebo and was well tolerated in the phase III REGARD study [22].

Based on the external evidence and our clinical experience, we would like to comment on the open questions that have been identified. Our motivation is to contribute to optimizing the use of taxanes in the treatment of adenocarcinomas of the stomach and EGJ.

Consensus on the Perioperative Setting

- Based on results from the FLOT-4 study, the use of the FLOT regimen is standard in the perioperative management of resectable gastric/EGJ cancer from stage 2A.
- Sufficient patient fitness is a requirement for the use of FLOT. The patient's chronological age is not the only decisive criterion for treatment decision-making.
- Geriatric assessment can provide some guidance on whether to administer FLOT in patients who are older than 70 years of age.
- The perioperative FLOT protocol is not suitable for unfit patients and patients with preexisting polyneuropathy.
- Possible options to be considered for borderline fit patients on an individual basis include both a de-escalation strategy (i.e., starting with FLOT and deescalating to FLO) or an escalation strategy starting with FLO and escalating to FLOT if the patient tolerates it. These procedures have not been validated in studies, however.
- Patients who are ineligible for treatment with FLOT should receive chemotherapy with a platinum-fluoropyrimidine doublet, e.g. the FLO (modified FOLFOX) protocol.
- Monotherapies however are not recommended in the perioperative setting.

Consensus on Palliative First-Line Treatment

- Quality-controlled HER2 testing prior to initiation of treatment according to recent recommendations [23] is mandatory for all patients scheduled for palliative therapy (stage 4).
- The current standard of care for patients with HER2-positive tumors is chemotherapy (platinum plus fluoropyrimidine) in combination with trastuzumab.
- The standard of care in HER2-negative tumors is a doublet chemotherapy regimen (platinum derivative plus fluoropyrimidine; a possible alternative being irinotecan plus fluoropyrimidine).

- Taxanes integrated in triplet regimens are no standard and should only be administered to selected patients with HER2-negative tumors, for example if there is strong pressure to achieve remission.
- Taxane-based protocols as first-line treatment are to be considered only for selected patients in good general health. The group of experts treat only 10–20% of their patients with a taxane-containing first-line regimen.
- In view of the significant increase in toxicity coupled with little to no improvement in patient-relevant outcomes, the use of taxanes in first-line advanced gastric or EGJ cancer requires a clear medical rationale. This may include a high tumor or symptom burden or very rapid tumor progression so that achieving a fast response is of special importance (e.g., because organ function might be impaired by high tumor load). "Conversion therapy" of initially not resectable tumors can be another valuable argument.
- To minimize the incidence of neuropathy, and in view of possible second-line treatment options, i.e. ramucirumab plus paclitaxel, a de-escalation strategy to limit the duration of taxane use should be considered.
- Side effects of taxane therapy such as neuropathy or taste abnormalities may be very distressful to patients even at severities not exceeding grade 1 or 2. Patients therefore need to be reevaluated for side effects before each treatment cycle.
- First-line taxanes for advanced disease should be administered only for as long as necessary, i.e. until the therapy goal has been reached (e.g., symptom control achieved or the pressure for remission has eased).
- For patients who received perioperative FLOT for locally advanced disease and relapse, reinduction therapy with FLO or FLOT is of uncertain value. Potential exception are patients with a relapse-free survival of ≥6 (better 12) months, a good clinical and histopathological response (at least Becker 1b), and no or minimal residual toxicities (e.g., neurotoxicity). FOLFIRI (irinotecan, 5-FU, leucovorin) is a preferred first-line alternative in this situation.
- Patients who receive taxanes for first-line treatment should be closely monitored. Clinical monitoring should take place regularly, with imaging to take place after every 6–12 weeks. Good patient compliance is a requirement for administering this regimen. Patients need to be informed of the necessity to report any complications promptly to their physician.

Consensus on Second-Line Treatment

- Ramucirumab plus paclitaxel is the recommended standard of care. Irinotecan-based treatments or ramucirumab monotherapy can be considered as alternative second-line treatment options for all eligible patients, including taxane-experienced patients, after prior platinum- and fluoropyrimidine-based chemotherapy.
- According to the current state of knowledge, ramucirumab plus paclitaxel may be administered for second-line treatment even after previous taxane-containing therapy. However currently available clinical trial data on the efficiency of taxanes after docetaxel failure are contradictory. Large informative studies are lacking.
- If required due to taxane-related toxicity, it is recommended to deescalate ramucirumab-paclitaxel combination therapy to ramucirumab monotherapy after a response or stable disease has been achieved, similar to the procedure followed in the REGARD study.
- Ramucirumab monotherapy, irinotecan, paclitaxel, and docetaxel are equivalent treatment options in terms of efficacy. Single-agent therapies should only be preferred in patients who do not tolerate standard ramucirumab-paclitaxel therapy or have contraindications to either of the two drugs.

Conclusions

Since the publication of several positive studies in second- and third-line therapy, sequential therapy is playing an increasing role in metastatic cancer of the stomach and EGJ. The authors discuss the use of taxanes in the perioperative and palliative chemotherapy sequence. This expert consensus is intended to contribute to rational and evidence-based sequential therapy in these cancers.

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