Review

Treatment Algorithm for Patients With Gastric Adenocarcinoma: An Austrian Consensus on Systemic Therapy

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Abstract. *Despite recent advances in the treatment of gastric cancer, mortality related to this disease is still substantial. Surgery and chemotherapy represent the cornerstones of patient management. Targeted treatments that include anti-angiogenic agents and the advent of immunotherapies can contribute to improved patient prognosis. Herein, we present an Austrian consensus on the systemic treatment of patients with gastric adenocarcinoma and lower gastroesophageal junction, including those with human epidermal growth factor receptor 2 (HER2)-positive disease. The consensus considers the curative setting, as well as first-line to late-line systemic treatment options in the palliative setting. For HER2-positive disease, first-line and second-line therapies are discussed, as well as HER2 testing. Potential future therapies are also listed, with a focus on anti-angiogenic treatments and checkpoint inhibition, that might provide a further step forward in the management of patients with gastric cancer.*

Gastric cancer is one of the more common malignant diseases worldwide, although its incidence continues to decrease in the western world (1). Patient prognosis depends on a number of factors, including disease stage and histology, patient performance status, and the presence of comorbidities. Early stages and locally restricted disease allow for treatment with curative intent, while a palliative approach is called for in the metastatic or locally advanced and inoperable settings. Treatment modalities can be defined as surgery and systemic. Despite the substantial progress that has been made over the past decade, cancer-related mortality remains high, at 70%.

This Austrian consensus on systemic therapy for gastric cancer was drawn up in the light of changes in perioperative management and new treatment options emerging for later lines. At an Expert Meeting that took place in Fuschl, Austria, on October 12, 2018, experts discussed a range of topics based on current treatment guidelines. The summary of the discussion is the basis of this treatment algorithm and replaces the previously published recommendations (2).

The recommendations discussed here are restricted to adenocarcinoma of the stomach and lower gastroesophageal junction (Siewert III).

This article is freely accessible online.

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Key Words: Gastric cancer, adenocarcinoma, stomach, lower gastroesophageal junction, treatment algorithm, review.

Curative Treatment

For patients with good Eastern Cooperative Oncology Group performance status (*i.e.* ECOG PS 0-1), implementation of a perioperative treatment plan is mandatory from stage IB

disease ($\geq T2$ or $N+$) onward. This necessitates preoperative discussion of each patient case by the Interdisciplinary Tumor Board. The first-choice treatment is perioperative chemotherapy according to the FLOT regimen [5-fluorouracil (5-FU), leucovorin, oxaliplatin, docetaxel] (3, 4). Data have demonstrated that responses to FLOT can be expected regardless of the histological subtype of the tumor (*e.g.* signet ring cell component *vs.* no signet ring cell component). Anthracycline-containing regimens such as epirubicin, oxaliplatin and capecitabine (EOX) and epirubicin, cisplatin with capecitabine (ECX) (5) have been shown not to be as effective and should not be used in the clinical setting. De-escalation strategies can be established once toxicities emerge.

The primary administration of granulocyte-colony stimulating factor along with FLOT is not mandatory, but it might be necessary in individual patients because the rate of neutropenia with FLOT can be as high as 50%. In the AIO FLOT-4 trial (716 patients included), 90% of the patients received four preoperative FLOT doses as planned, but only 51% completed the four planned postoperative doses. Comorbidities and pre-existing neuropathy can impede or preclude the use of FLOT (3).

Alternative regimens for patients intolerant to FLOT include platinum-based doublets, such as modified FOLFOX or 5-FU, and leucovorin and oxaliplatin. In older patients, intravenous 5-FU offers advantages over oral treatment. In the FLOT study, addition of taxanes provided distinct benefits (3). However, findings in Asia from the JACCRO GC-07 phase III trial were not as clear-cut (6). Here, the difference between S-1/docetaxel and S-1 alone for relapse-free survival was significantly in favor of S-1/docetaxel, while the overall survival (OS) difference was not. However, these data do not influence treatment decisions for Caucasian patients. The interval between the last chemotherapy and surgery should be 4 to 6 weeks.

Although patients with ECOG PS >1 were not included in the FLOT study, there was no age limit, with a median age of 65 years. Therefore, age was not a decisive factor here. FLOT should be offered to patients with stage IB disease ($\geq T2$ or $N+$) or higher who have ECOG PS 0 or 1. As trial data are lacking for patients with ECOG PS 2, the choice of treatment needs to be determined on an individual basis. If tumor-related symptoms are the cause of poor patient ECOG PS, this justifies an aggressive perioperative approach. Patients whose condition precludes treatment with a doublet regimen should primarily undergo surgery. It is important not to jeopardize surgery as a result of intensive neoadjuvant therapy. As the validity of the ECOG PS has limitations, the modified Frailty Score Index (7) can be helpful for estimation of the overall condition of an individual patient in clinical practice, although it has not been formally tested in preoperative studies.

In the primarily curative setting, adjustment of the subsequent treatment is called for only if progression occurs

within 6 months, as this implies that the perioperative treatment counts as the first line of the palliative regimen. Persistent neuropathy can influence the choice of the subsequent therapy.

For patients who do not develop postoperative complications, the interval between surgery and the next follow-up visit in clinical practice is commonly 2 to 3 weeks. Ideally, no more than 4 to 6 weeks should elapse until the start of postoperative chemotherapy. If the patient's recovery within 2 months is not sufficient to allow for chemotherapy, a watch-and-wait strategy can be considered.

The degree of histological regression after neoadjuvant treatment does not affect the selection of the postoperative regimen. Furthermore, the treatment should be continued postoperatively irrespective of the degree of regression that has been achieved. Rather, patient fitness is the crucial factor that determines the next steps. No data have been obtained for treatment changes nor treatment discontinuation based on the degree of regression.

It can be assumed that the efficacy of the treatment is mainly based on the neoadjuvant part, as almost half of all patients are unable to complete their postoperative therapy (5, 8). Responses to neoadjuvant treatment should be viewed as prognostic rather than predictive. First and foremost, the perioperative therapy targets micrometastatic disease after removal of the primary tumor. The degree of regression might therefore be a surrogate marker for treatment efficacy with respect to metastases; however, this assumption needs to be explored in a prospective manner. Patients who undergo curative surgery and only experience disease stabilization with FLOT therapy should continue treatment.

Nowadays, patients who do not receive chemotherapy prior to the resection of their tumors should be the exception. Adjuvant chemotherapy can be offered to patients with locally advanced gastric cancer who have not received preoperative treatment as a result of their insufficient staging (9). Caucasian patients do not benefit from intensified postoperative chemotherapy (10, 11). Moreover, no evidence is available on the ideal number of cycles; clinical trials have suggested treatment durations of 6 months and up to 1 year in Caucasian and Asian patients, respectively (12).

Combined radiochemotherapy is an option after insufficient lymph node dissection in the context of emergency surgery (13). Patients who have undergone adequate lymph node dissection (D1+, 2) and have not received preoperative therapy can be offered postoperative adjuvant chemotherapy. Based on published data, it appears that only patients who undergo inadequate lymph node resection will benefit from combined radiochemotherapy (9, 14, 15). With respect to the type of chemotherapy, the only data available in the postoperative setting were obtained for fluoropyrimidine. The ARTIST trial investigated adjuvant chemotherapy *versus* concurrent chemoradiotherapy and did

not show a difference in disease-free or overall survival. The subgroup of patients with node-positive disease who simultaneously underwent D2 dissection, however, showed improved disease-free survival (16).

Overall, the available evidence does not support solid recommendations concerning the role of radiotherapy in gastric cancer. Data from randomized studies will provide future information, although only on the comparison between combined radiochemotherapy and perioperative chemotherapy. For the time being, combined radiochemotherapy is an option for patients who have undergone primary surgery with inadequate lymph-node dissection; for those with adequate resection, no data-pool exists.

Ongoing phase III studies, from which the results are awaited, are investigating radiochemotherapy for gastroesophageal junction tumors. Until these are completed, patients with gastroesophageal junction tumors can be offered both radiochemotherapy and chemotherapy (8, 17). Moreover, in the human epidermal growth factor receptor 2 (*HER2*)-positive setting, ongoing phase III trials are evaluating chemotherapy plus trastuzumab and pertuzumab. In *HER2*-negative patients, chemotherapy plus ramucirumab is being tested (NCT02661971), as well as chemotherapy plus immune checkpoint inhibitors (NCT03221426). No statement can be made about these strategies at present.

Palliative Setting

HER2 testing as a prerequisite for palliative therapy. The therapy used for patients with advanced inoperable gastric cancer or metastatic gastric cancer is driven by their *HER2* status. Patients with *HER2* positivity defined by immunohistochemistry (*i.e.* IHC 3+ or IHC 2+) and positive by fluorescence or silver *in situ* hybridization are treated differently (see below). *HER2* testing is therefore mandatory for these patients, although it is generally difficult due to the heterogeneity of tumors and the quality of the pre-analytics. Analysis of the Austrian GASTRIC-5 registry has revealed variations of ~17% with respect to *HER2* readings (18). Therefore, certified or quality-assured testing is called for. Pathologists should participate in inter-laboratory comparison trials, or ring trials, and strive for high-quality processing of their samples.

First-line treatment of HER2-negative disease. Treatment is indicated for patients with ECOG PS ≤2. Patients with ECOG PS >2 should only be considered for treatment if their PS deterioration is actually tumor-related.

Several studies have compared triplets with doublets in the frontline setting for patients with *HER2*-negative disease. Triplets have provided higher response rates than doublets; however, for OS, the differences have been markedly less pronounced, while at the same time, triplet therapies have

considerably higher toxicity rates. Therefore, the trend observed toward improved OS must be weighed against the adverse effects of these treatments. Improvements to progression-free survival (PFS) and OS that are obtained at the expense of tolerability to the treatment often do not appear justified in the palliative setting. As a consequence, doublets are generally preferred for palliative first-line therapy in clinical practice. The benefits that can be obtained from triplets can be expected in patients who are highly symptomatic or who require a rapid response due to a high tumor burden (9, 19). In all other patients, doublets should be preferred (9, 20, 21). Monotherapy is an exception; if a patient is not fit enough to receive doublet chemotherapy, the question must be raised as to whether systemic treatment is appropriate in the first place.

Patient age, as such, is not a criterion for clinical decisions. It has been shown that FLOT can be used in older patients, albeit only in those who are deemed fit and who need a rapid response. FLOT or modified docetaxel, cisplatin and 5-FU (DCF) have greater practicability and exhibit less toxicity, and these should therefore be preferred to standard DCF. The available doublets comprise platinum-containing combination regimens including oral or intravenous fluoropyrimidine. Here, the FLO regimen has primarily been explored in older patients (22). For patients for whom platinum-containing treatments are contraindicated, phase III data have established 5-FU, leucovorin combined with irinotecan (FOLFIRI) as an alternative (11). Platinum combinations boast a greater wealth of data. In patients with pronounced neuropathy, which limits the use of platinum therapy, FOLFIRI is a valid option. Anthracycline-containing triplets (*e.g.* epirubicin, cisplatin, 5-FU, ECX) play a minor role, due to the increased likelihood of adverse events.

If no toxicity issues are expected, repeated administration of taxanes represents an option in the relapse setting, as long as they are accompanied by an adequate time interval after perioperative (curative) pretreatment, which should be at least 3 to 6 months. Grade 1 neuropathy is not a contraindication; however, the accuracy of the medical history examination greatly influences grading, in terms of the degree of limitations in the daily life of the patient.

Dual treatment with capecitabine plus oxaliplatin (CAPOX) or FOLFOX can replace FLOT for patients who do not require rapid response. However, in patients whose disease progresses within 3 months of perioperative FLOT administration, the treatment should be switched to FOLFIRI or to other second-line options (see below).

First-line treatment of HER2-positive disease. Assessment of *HER2* status is generally performed at the time of the initial diagnosis of gastric cancer. Trastuzumab plus platinum/fluoropyrimidine-containing chemotherapy doublets is the standard first-line treatment of *HER2*-positive gastric cancer.

In addition to trastuzumab, platinum and fluoropyrimidine are recommended as backbones for first-line treatment. CAPOX, FLO, FOLFOX, and cisplatin/5-FU are commonly used in clinical practice, whereas cisplatin/capecitabine is less popular (23). Trastuzumab is administered intravenously. Chemotherapy should be limited to a maximum of six cycles, while trastuzumab treatment should be continued until progression (24).

In the perioperative setting, the use of trastuzumab is still under investigation, so the results of ongoing trials are awaited. One issue, however, is the omission of preoperative laparoscopy in patients with localized, *HER2*-positive gastric cancer who receive preoperative FLOT with curative intent, as the presence of peritoneal carcinomatosis requires palliative trastuzumab treatment. The incidence of peritoneal carcinomatosis increases steeply from stage T2 onwards; therefore, preoperative laparoscopy is recommended in these patients.

Second-line treatment of HER2-negative disease. Based on phase III data, ramucirumab plus paclitaxel constitutes the favored second-line strategy for *HER2*-negative disease (25). Other available options include single-agent options of ramucirumab (26), irinotecan (27, 28), docetaxel (29), and paclitaxel (28, 30). The most effective second-line therapy is the combination of ramucirumab and paclitaxel (25). Alternatively, the single-agent option of docetaxel [COUGAR trial (29)] or remucirumab (19) can be selected if toxicity of the combination is projected.

Ramucirumab monotherapy appears feasible for frail patients because of its favorable toxicity profile, although these patients have not been included in the phase III trials (31). Contraindications for ramucirumab include cardiovascular disease, increased thrombotic risk, and oral anticoagulation. If there are contraindications, single-agent taxanes or irinotecan can be used, whereby the adverse event profiles of these drugs will determine the choice of treatment. Diarrhea precludes the administration of irinotecan, while taxanes should not be used for patients with neuropathy grade >1. There is solid evidence that only patients with good performance status benefit from second-line treatments. No specific statements can be made for patients with poor performance status, as these patients were not included in the trials (25-29, 31).

Switching between docetaxel and paclitaxel as first-line and second-line treatments might be an option, as there is no complete cross-resistance between the two taxanes. Potential solutions include the interposing of irinotecan into the second-line treatment, as well as a time interval of at least 6 months.

Second-line treatment of HER2-positive disease. The continuation of trastuzumab treatment beyond progression is not an established approach in gastric cancer due to a negative randomized trial (32). Reductions in *HER2*

overexpression are most likely due to the selection of *HER2*-negative clones after first-line treatment with trastuzumab (33, 34). Rechallenge of trastuzumab after tumor progression in individual patients can only be based on a second positive *HER2* test prior to treatment but is not supported by prospective data (32).

Therefore, the second-line treatment of *HER2*-positive patients is currently the same as that of *HER2*-negative patients.

Third-line treatment. Results from the clinical phase III trial TAGS have demonstrated that trifluridine/tipiracil is an active third-line option that will not induce response, but can provide disease stabilization along with significant PFS and OS benefits (35, 36). This has led to approval of this drug by the U.S. Food and Drug Administration, while this option was submitted for approval to the European Medical Association. Trifluridine/tipiracil has been in use in the colorectal cancer setting for a long time; its use is thus well established, and it is easy to handle. Therefore, trifluridine/tipiracil is a valid option in patients with progressive disease in later lines with ECOG PS of 0 or 1.

The ATTRACTION-2 trial demonstrated superiority of nivolumab over placebo, thus introducing nivolumab as another third-line option. The limitations of ATTRACTION-2 included the exclusive Asian origin of the study population. Moreover, the vast majority of these patients had been diagnosed with gastric carcinoma, and they had very good performance status (37).

In Caucasians, trifluridine/tipiracil was investigated in a patient group that had received comparatively fewer previous treatment lines, which better reflects European use. Trifluridine/tipiracil appears to be a favorable option for the all-comer population, which obviously benefits less from checkpoint inhibition than biomarker-selected patients. The biomarkers here include programmed death-ligand 1 (PD-L1), high-level microsatellite instability (MSI-H), and combined positivity score (CPS) ≥ 10 (38, 39). However, checkpoint inhibitors are an alternative in this setting. Emerging data indicate heightened responses to certain checkpoint inhibitors in selected patient groups, *i.e.* those with MSI-H, Epstein-Barr virus-associated tumors, high PD-L1 expression, CPS >10 , and high tumor mutational burden. In these groups, checkpoint inhibition might be an option even in the early treatment lines, although trial data are lacking. The KEYNOTE-061 and JAVELIN Gastric 300 trials yielded negative results for the comparison of checkpoint inhibitors with established chemotherapy regimens as second-line treatments for unselected patients (40, 41). In KEYNOTE 061, however, the subgroup of patients with high CPS benefited from checkpoint inhibition.

The pivotal phase III trial KEYNOTE-062 evaluated pembrolizumab as monotherapy and in combination with

chemotherapy (cisplatin and either 5-fluorouracil or capecitabine) for the first-line treatment of advanced gastric or gastroesophageal junction adenocarcinoma. In the monotherapy arm of the study, pembrolizumab met a primary endpoint by demonstrating noninferiority to chemotherapy, the current standard of care, for OS in the intention-to-treat population of patients whose tumors expressed PD-L1 (CPS ≥ 1). In the combination arm, pembrolizumab plus chemotherapy was not found to be superior for OS (CPS ≥ 1 or CPS ≥ 10) or PFS (CPS ≥ 1) compared with chemotherapy alone (42).

In patients with gastric carcinoma, CPS is assessed at certain clinics, while tumor mutational burden is not assessed routinely. The choice of immunotherapy can be based on immune cell positivity or CPS. MSI and the PD-L1 status are easy to assess and are reproducible. Reports show that analysis using polymerase chain reaction is more sensitive in gastric carcinoma than immunohistochemistry; therefore, this is the only situation in which polymerase chain reaction might be used as an add-on to MSI testing. In other tumor types, immunohistochemistry is sufficient. Double assessment using immunohistochemistry and sequencing is common.

Microsatellite instability testing is more important for treatment decisions in the second line than the first line; this can play a role in Tumor Board treatment decisions. In later lines, MSI testing has great importance. MSI assessment does not require specialized centers (43, 44).

The experts reported no personal experience or study experience regarding hyperprogression, which occurs infrequently during checkpoint inhibitor therapy for gastric cancer. In contrast, assessment of remission can be difficult due to pseudo-progression.

Conflicts of Interest

Wöll E.: speaker and advisory fees: Amgen, Astra Zeneca, BMS, Celgene, Ebewe, Eisai, Eli Lilly, Janssen Cilag, Merck, MSD, Pfizer, Ratiopharm, Roche, Sanofi Aventis. Prager G.: Advisory Board: Merck, Serono, Roche, Amgen, Sanofi, Lilly, Servier, Taiho, Bayer, BMS, Celgene, Shire; Institutional financial interests-Clinical Trials: Celgene, Array, Servier, Bayer, BostonBiomedical, Merck, BMS. All other Authors declare no conflict of interest in regard to this study.

Authors' Contributions

Conception and design: Wöll E; Data analysis and interpretation: All Authors contributed equally; Manuscript writing: Wöll E; Final approval of article and corrections: All Authors contributed equally.

Acknowledgements

The Authors thank Dr. Judith Moser for providing writing assistance. Publication of this review was supported by a grant of Verein für Tumorforschung.

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Received June 2, 2019

Revised July 15, 2019

Accepted July 19, 2019