ANTICANCER RESEARCH *43*: 2889-2897 (2023)
doi:10.21873/anticanres.16460

Review

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

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Abstract. *Over the last decade, therapeutic options for patients with gastric cancer have improved significantly. However, despite these recent advances, mortality is still substantial. Surgery and chemotherapy represent the cornerstones of patient management. Immune checkpoint inhibitors as well as targeted treatments such as HER2-directed therapies and antiangiogenic agents contribute to improved patient prognosis. Herein, we present the updated version of an Austrian consensus on the systemic treatment of patients with gastric adenocarcinoma and adenocarcinoma of the lower gastroesophageal junction, including those with human epidermal growth receptor 2 (HER2) overexpression, microsatellite instability, programmed death-ligand 1 (PD-L1)–positive disease, and claudin 18.2 positivity. The consensus considers the curative setting as well as first-line and later-line systemic treatment options in advanced disease. For HER2-positive disease, HER2 testing is discussed in addition to a review of first-line and later-line therapies. Potential future therapies are also listed, with a focus on targeted [e.g., fibroblast growth factor receptor 2 (FGRF2)-directed] treatments that might provide a further step forward in the management of patients with gastric cancer.*

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

From the global point of view, gastric cancer is still one of the most common malignancies, although its incidence is continuously decreasing in western countries (1). Various factors including disease stage and histology, patient performance status, as well as the presence of comorbidities determine patient prognosis. Whereas curative treatment is possible in early stages and localized disease, palliative measures must be applied in the setting of metastatic or locally advanced and inoperable gastric cancer. Treatment modalities comprise surgical and systemic approaches. Although the management of patients with gastric cancer has substantially improved over the past decade, the cancer-related mortality is still as high as 70%.

The Austrian consensus on systemic therapy for gastric cancer was compiled against the background of recent changes in the perioperative management and the emergence

of new later-line treatment options. The first version published in 2019 was based on an Expert Meeting that took place in Fuschl, Austria, in October 2018 (2). This expert recommendation that summarizes the discussions conducted at the follow-up meeting in Salzburg, Austria, in October 2022, replaces the previously published version. The recommendations detailed here are confined to adenocarcinoma of the stomach and lower gastroesophageal junction (Siewert type III).

Curative Treatment

For patients with good Eastern Cooperative Oncology Group performance status (*i.e.*, ECOG PS 0-1), implementation of a perioperative treatment plan including diagnostic laparoscopy in individuals with high risk of peritoneal carcinomatosis (*e.g.*, diffuse type, high grading, lymph node positivity) is mandatory from stage IB disease (≥T2 or N+) onward, which implies that each case should be discussed preoperatively by the multidisciplinary Tumor Board. Perioperative chemotherapy according to the FLOT regimen [*i.e.*, 5-fluorouracil (5-FU), leucovorin, oxaliplatin, docetaxel] is the treatment of choice in stage IB or higher (3, 4). FLOT can be expected to elicit responses irrespective of the histological subtype, for instance regarding the presence or absence of a signet ring cell component. Due to their comparably lower efficacy, anthracycline-containing regimens such as epirubicin, cisplatin and capecitabine (ECX) or epirubicin, oxaliplatin and capecitabine (EOX) (5) should not be used.

Comorbidities and pre-existing neuropathy can hamper or prevent the administration of FLOT (3). Although primary granulocyte-colony stimulating factor support is not imperative in the context of FLOT therapy, it might prevent treatment delays in the high-risk setting as FLOT gives rise to neutropenia rates of up to 50%. An example of this is the AIO FLOT-4 study in which 90% of patients received the four planned preoperative FLOT doses whereas only 51% completed the four postoperative doses. Toxicities can be managed using de-escalation strategies. For patients intolerant to FLOT, an alternative strategy is the use of platinum-based doublets including modified FOLFOX, CAPOX or FLO (5-FU, leucovorin, oxaliplatin). Intravenous 5-FU offers advantages over oral treatment in the elderly.

While the addition of taxanes proved beneficial in the FLOT study, results were less unequivocal in the Asian phase III JACCRO GC-07 trial where S-1/docetaxel, as compared to S-1 monotherapy, significantly prolonged relapse-free survival but not overall survival (OS) (3, 6). Nevertheless, treatment decisions in Caucasian patients are not necessarily affected by these insights. The interval between chemotherapy and surgery should be 4 to 6 weeks.

The design of the FLOT study precluded the enrollment of patients with ECOG PS >1. However, the absence of an age limit led to a median patient age of 65 years, due to which age did not represent a decisive factor. Therefore, FLOT should be offered to patients with ECOG PS 0 or 1 and stage IB disease (≥T2 or N+) or higher. In the group with ECOG PS 2, treatment decisions need to be individualized considering the lack of trial data. An aggressive perioperative approach is justified in patients whose poor ECOG PS can be assumed to be due to tumor-related symptoms. If the patient's condition precludes the administration of a doublet regimen, primary surgery should be performed. The tumor resection takes precedence over any benefits potentially induced by intensive neoadjuvant therapy and should not be put at stake. In addition to the ECOG PS, the modified Frailty Score Index (7) can be used to assess the overall patient condition, although formal testing in preoperative studies has not been performed to date.

The subsequent treatment should only be adjusted in the primarily curative setting if progression occurs within 6 months; in this case, the perioperative therapy counts as the first palliative treatment line. Persistent neuropathy can affect the selection of subsequent regimens. In clinical practice, the first postoperative follow-up visit in patients who did not develop complications usually takes place 2 to 3 weeks after surgery. The interval between surgery and postoperative chemotherapy should not exceed 4 to 6 weeks. In patients who do not appear to be up to postoperative chemotherapy within 2 months of surgery, a watch-and-wait strategy can be considered. The selection of postoperative treatment is independent of the degree of histological regression that has been achieved with neoadjuvant chemotherapy, as no evidence has been generated concerning treatment adjustments based on histological changes. Rather, patient fitness determines the next steps.

Presumably, the benefits of the perioperative treatment rest mainly 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. As the perioperative therapy primarily targets micrometastatic disease after the removal of the tumor, the degree of regression might represent a surrogate marker for the efficacy of treatment with respect to dissemination. Nevertheless, prospective data are required to confirm this assumption. Patients receiving FLOT who only experience disease stabilization after curative surgery should continue treatment.

By current standards, omission of chemotherapy prior to the resection of gastric cancer should remain an exception. Adjuvant chemotherapy can be offered to patients with locally advanced tumors who have not undergone preoperative treatment due to insufficient staging (9). Data show that Caucasian patients do not benefit from intensified postoperative chemotherapy (10, 11). The ideal number of cycles is unknown. According to clinical trials, treatment should be performed for 6 months and up to 1 year in Caucasian and Asian patients, respectively (12).

Postoperative chemotherapy can be dose-reduced or administered as doublet therapy dependent on the expected side-effect profile and patient performance status. Forthcoming data will demonstrate the excellent prognosis of patients with ypN0 tumors, which might lead to further adaption of the adjuvant approach. In patients who show unambiguous progression according to RECIST that is clearly locoregional, adjuvant treatment can be omitted after R0 resection has been achieved.

Combined radiochemotherapy can be considered in patients who underwent emergency surgery and received insufficient lymph node dissection (13). After adequate lymph node dissection (D1+, 2) without preoperative therapy, postoperative adjuvant chemotherapy can be offered. Published data imply that combined radiochemotherapy is only beneficial in the setting of inadequate lymph node resection (9, 14, 15). Concerning the type of postoperative chemotherapy, data were obtained for fluoropyrimidine only. The ARTIST trial did not show differences regarding disease-free survival or OS between adjuvant chemotherapy and concurrent chemoradiotherapy. However, the cohort of patients with node-positive disease who simultaneously underwent D2 dissection experienced increases in disease-free survival (16).

Overall, no solid recommendations with respect to the role of radiotherapy in gastric cancer can be provided based on the available evidence. The randomized AIO RACE (NCT04375605) and ESOPEC (NCT02509286) trials are currently testing combined radiochemotherapy against perioperative chemotherapy. For the time being, it can be stated that combined radiochemotherapy is an option after primary surgery with inadequate lymph-node dissection, whereas no data pool has been established to date for patients after adequate resection.

Ongoing phase III studies are comparing radiochemotherapy for gastroesophageal junction tumors to perioperative chemotherapy. Until these trials are reported, patients with gastroesophageal junction tumors can be offered either neoadjuvant radiochemotherapy or perioperative chemotherapy (8, 17). Certain settings in the context of gastroesophageal junction cancers (*e.g.*, stenosing, locally extensive tumors) may require neoadjuvant chemoradiotherapy followed by surgery according to the Tumor Board decision, although FLOT will constitute the more feasible option in the majority of cases. If no pathologic complete response (pCR) has been obtained upon chemoradiation, patients should receive adjuvant treatment with nivolumab for 1 year. The randomized, phase III CheckMate 577 trial has demonstrated doubling of disease-free survival with nivolumab *versus* placebo in patients who showed residual pathologic disease (*i.e.*, ≥ ypT1 or ≥ ypN1) after R0 resection of stage II/III esophageal or gastroesophageal junction cancer following neoadjuvant chemoradiotherapy (18).

Regarding the role of immunotherapy in the curative setting, the treatment landscape is changing, and studies are ongoing. Data will emerge for the all-comer setting and for patients with combined positive scores (CPS) of 1-10. Controversial evidence exists on the benefit in patients with high-level microsatellite instability (MSI-H) who receive chemotherapy. As trials show consistently high pCR rates in the absence of phase III data, these cases should at least be discussed by the Tumor Board. Chemotherapy plus checkpoint inhibition might represent a valuable option here.

In the human epidermal growth factor receptor 2 (*HER2*)-positive setting, the phase II PETRARCA trial has established superiority of the combined administration of trastuzumab and pertuzumab together with perioperative chemotherapy compared to chemotherapy alone, with tripling of the pCR rate (19). However, the results of the three-arm, phase II INNOVATION trial that is assessing chemotherapy alone or in addition to trastuzumab or pertuzumab/trastuzumab, need to be awaited before any final statement can be made (NCT02205047).

In *HER2*-negative patients, chemotherapy plus ramucirumab is being investigated (NCT02661971), which also applies to chemotherapy in addition to immune checkpoint inhibition. No statement can currently be made about these approaches.

Palliative Setting

Testing as a prerequisite for palliative therapy. Molecular profiling is increasingly important in the treatment of patients with advanced inoperable or metastatic gastric cancer. In addition to the *HER2* status, testing of the CPS and MSI status is mandatory, and testing of claudin 18.2 should be encouraged. Whenever possible, patients with advanced gastric cancer should be enrolled in clinical trials.

Patients with *HER2* positivity defined by immunohisto-chemistry (*i.e.*, IHC 3+ or IHC 2+ and positivity by fluorescence or silver *in situ* hybridization) are treated differently (see below). In clinical practice, reliable HER2 test results are not easy to obtain due to factors such as the heterogeneity of tumors and the variable quality of pre-analytics. Indeed, data from the Austrian GASTRIC-5 registry have demonstrated variations of HER2 readings of approximately 17% (20). Measures that can increase the diagnostic accuracy include certified or quality-assured testing and the participation in inter-laboratory comparison trials, or ring trials. Pathologists should strive for high-quality processing of their samples.

First-line treatment of HER2-negative, PD-L1 CPS <5 disease. Treatment is indicated for patients with ECOG PS ≤2, whereas those with ECOG PS >2 should only be considered for treatment if the deterioration of their performance status is tumor-related.

In the HER2-negative setting, studies have investigated the frontline use of triplets *vs*. doublets. Triplets have been shown to be superior regarding response rates, whereas the OS differences have been considerably less pronounced. At the same time, toxicity was markedly increased with triplet regimens. This suggests that the trend toward improved OS observed with intensive treatment must be weighed against the side effects. Particularly in the palliative setting, progression-free survival (PFS) and OS gains achieved at the expense of tolerability might not appear justified, which is why doublets are generally preferred for palliative first-line treatment. Patients who are likely to benefit from triplets include those with highly symptomatic disease or the need for rapid responses due to high tumor burden (9, 21). Doublets should be the treatment of choice in all other cases (9, 22, 23). In patients who are not fit enough to tolerate doublet chemotherapy, systemic treatment might not be appropriate in the first place; single-agent approaches should thus remain exceptional.

Patient age *per se* is not a criterion for clinical decisions. Among the available doublets, which comprise platinum-containing combinations including oral and intravenous fluoropyrimidine, the FLO regimen has primarily been assessed in elderly patients (24). Although platinum combinations boast a greater wealth of data, 5-FU and leucovorin combined with irinotecan (FOLFIRI) represents an alternative in patients with contraindications for platinum-containing approaches such as pronounced neuropathy (11). Based on phase III evidence, FOLFIRI is a valid option in this situation.

First-line treatment of HER2-negative, PD-L1 CPS ≥5 disease. In patients with PD-L1 CPS ≥5 or MSI-H tumors, combined chemoimmunotherapy according to the randomized phase III CheckMate 649 study is recommended. CheckMate 649 has shown improved OS and PFS for nivolumab plus XELOX or FOLFOX compared to chemotherapy alone in patients with PD-L1 CPS ≥5. The improvement of response rates, however, is independent of PD-L1 CPS (25). Based on this observation, all-comers who are in need of rapid remission are candidates for nivolumab plus doublet chemotherapy as an alternative to triple chemotherapy. Patients with MSI-H tumors who are not fit for chemotherapy can receive immunotherapy only.

Another regimen feasible for patients with Siewert I cancers and PD-L1 CPS ≥10 is pembrolizumab plus 5-FU and cisplatin as assessed in the phase III KEYNOTE-590 trial (26). The evidence generated here is somewhat weaker than that for CheckMate 649 as only a very small number of patients with Siewert type I adenocarcinoma was included. If checkpoint inhibitors have not been used in the first-line setting in MSI-H tumors, they should be prescribed as early as possible in subsequent lines. This applies particularly to pembrolizumab that has received tumor-agnostic approval by the European Medicines Agency (EMA).

First-line treatment of HER2-positive disease. *HER2* testing is generally part of the baseline assessments performed at the initial diagnosis of gastric cancer. In patients with *HER2*-positive disease, the standard first-line treatment consists of trastuzumab plus platinum/fluoropyrimidine-containing chemotherapy doublets. While CAPOX, FLO, FOLFOX, and cisplatin/5-FU are commonly used in clinical practice, cisplatin/capecitabine is less popular (27). The treatment duration of chemotherapy should not exceed 6 months; on the other hand, trastuzumab treatment is continued until progression (28).

With respect to immunotherapy, the KEYNOTE-811 trial has shown higher response rates with pembrolizumab plus trastuzumab and 5-FU/cisplatin or CAPOX *versus* trastuzumab plus chemotherapy alone in *HER2*-positive PD-L1 all-comers (29). These findings are highly relevant for patients who require rapid remission, and they have led to the approval of pembrolizumab plus trastuzumab by the FDA. Data on PFS and OS need to be awaited before final conclusions can be drawn. Based on a Tumor Board decision, however, the addition of pembrolizumab to chemotherapy and trastuzumab can be suggested in patients in need of a very rapid and deep response.

First-line treatment of HER2-negative, claudin-18.2–positive disease. In patients with claudin-18.2–positive tumors, combined treatment with mFOLFOX6 plus zolbetuximab, according to the randomized phase III SPOTLIGHT study, can be recommended, if available. This study has shown improvement in PFS, which was defined as the primary endpoint, and OS, while response rates did not improve (30). Particularly patients with claudin-18.2–positive tumors arising from the stomach experienced superior outcomes with zolbetuximab plus mFOLFOX6. Nausea and vomiting represented the most frequent treatment-emergent adverse events and occurred during the first zolbetuximab cycle.

Also, the clinical phase III GLOW trial (NCT03653507) investigating zolbetuximab plus CAPOX in the setting of locally advanced or metastatic claudin-18.2–positive gastric or gastroesophageal junction carcinoma was announced to be positive, although no data have been presented to date. Based on the SPOTLIGHT trial findings, claudin 18.2 testing should be rapidly incorporated into standard baseline pathological assessments.

Second-line treatment of HER2-negative disease. Phase III data have established ramucirumab plus paclitaxel as the favored second-line strategy for patients with *HER2*-negative gastric cancer (31). Those who do not qualify for doublet therapy, other available options include single-agent ramucirumab (32), irinotecan (33, 34), docetaxel (35), or paclitaxel (34, 36). Ramucirumab plus paclitaxel constitutes the most effective

second-line regimen (31). Alternatively, when this combination is expected to show toxicity, docetaxel [COUGAR trial (35)] or ramucirumab (21) can be used as single agents.

Single-agent ramucirumab appears to be a feasible option for frail individuals due to its favorable toxicity profile, although trial evidence is lacking here as these patients have not been enrolled in phase III studies (37). Relative contraindications for ramucirumab include uncontrolled cardiovascular disease, increased thrombotic risk, and oral anticoagulation. Single-agent taxanes or irinotecan represent alternative options in case of contraindications, with their toxicity profiles determining the treatment decisions. Diarrhea precludes the use of irinotecan, while taxanes should not be administered to patients who harbor neuropathy grade >1. Solid evidence indicates that benefits from second-line regimens can only be expected in patients with good performance status. As those with poor performance status were not enrolled in the trials, no specific statements can be made here (31-35, 37).

Considering the lack of complete cross-resistance between the two taxanes, switching between docetaxel and paclitaxel in the first and second lines appears feasible. Other options include the interposition of irinotecan in the second line and treatment intervals of at least 6 months.

The RAMIRIS phase II/III trial is investigating FOLFIRI plus ramucirumab *versus* paclitaxel plus ramucirumab. The phase II data obtained from this study are very promising and have shown feasibility and efficacy of ramucirumab plus FOLFIRI compared to ramucirumab plus paclitaxel (38). Phase III results are still pending, however. This approach might be an option in patients who have progressed within 3 months after taxane-based first-line therapy or perioperative FLOT, and in patients suffering from grade ≥2 polyneuropathy.

Second-line treatment of HER2-positive disease. Trastuzumab treatment beyond disease progression is not an established approach in gastric cancer owing to a negative randomized trial (39). *HER2* overexpression can lessen over time, which is most likely due to the selection of *HER2*-negative clones in the course of first-line therapy with trastuzumab (40, 41). Trastuzumab rechallenge after progression in individual patients requires the confirmation of sustained *HER2* positivity prior to treatment initiation but is not supported by prospective data (39).

Therefore, the second-line treatment recommended for *HER2*-positive patients is currently identical with that recommended for *HER2*-negative patients. Ramucirumab plus paclitaxel represents the preferred second-line option in patients who have not been retested.

Patients who show *HER2* overexpression are candidates for the antibody-drug conjugate trastuzumab deruxtecan based on the phase II DESTINY-Gastric02 study that has revealed impressive results in western patients (42). The phase III DESTINY-Gastric04 trial assessing trastuzumab deruxtecan in patients who progressed on or after a trastuzumab-containing regimen is still recruiting (NCT04704934). Nevertheless, approval of trastuzumab deruxtecan in patients with advanced *HER2*-positive gastric or gastroesophageal adenocarcinoma after a prior trastuzumab-based regimen has been granted by the EMA in December 2022.

Third-line treatment. The clinical phase III TAGS trial has shown that trifluridine/tipiracil is an active third-line option which does not induce responses but can provide disease stabilization along with significant PFS and OS improvement (43, 44). This has prompted the approval of this compound by the EMA in 2019 for patients with metastatic gastric cancer or gastroesophageal junction adenocarcinoma after at least two systemic regimens for advanced disease. As trifluridine/tipiracil has been in use in the treatment of colorectal cancer for years, its use is well established, and it is an easy-to-handle therapy. Therefore, this is a valid later-line option in patients with progressive disease and ECOG PS of 0 or 1.

In later treatment lines, reinduction of previously active therapies represents an option in patients with appropriate performance status that allows for continued treatment. Moreover, regimens can be considered that have not been used previously, *e.g.*, single-agent irinotecan.

Rare Subgroups and Future Perspectives

Comprehensive molecular testing using next generation sequencing and Epstein-Barr virus testing is potentially helpful, as well as discussion of patients in the molecular tumor board who qualify for further treatment after the established options have been exhausted. Although *NTRK* positivity is rare in patients with gastric cancers, the targeted agents larotrectinib and entrectinib have received tumor-agnostic approval and can be used in this setting.

Positive data on additional predictive markers such as FGFR2b have been reported for first-line therapy in phase II trials. FGFR2b overexpression is found in up to 30% of gastric and gastroesophageal junction adenocarcinoma cases. The addition of bemarituzumab, a monoclonal antibody directed against FGFR2b, to chemotherapy has shown improved OS at the phase II level (45). Two ongoing phase III trials, FORTITUDE 101 (NCT05052801) and FORTITUDE 102 (NCT05111626), will provide further information in the near future.

Conflicts of Interest

Wöll E has received speaker honoraria from Amgen, Astella Pharma, Astra Zeneca, BMS, Celgen, Daiichi Sankyo, Ebewe, Eisai, Eli Lilly, Elsevier, Janssen Cilag, Merck, MSD, Novartis, Pierre Fabre, Pfizer, Ratiopharm, Roche, Sanofi Aventis and Servier, Takeda. Gerger A has

received speaker honoraria from Amgen, Roche, BMS, MSD, Daichi Sankyo, Lilly, Merck, Pierre Fabre, Servier and Consulting fees from Merck, MSD; Research Support: Roche, MSD, BMS and Amgen. Weiss L has received speaker honoraria from Amgen, Astellas, BMS, Daichi Sankyo, GSK, Lilly, Merck, MSD, Novocure, Pharmamar, Pierre Fabre, Roche, Servier and consulting fees from Merck and MSD. He has also received research Support from Novocure, Roche and Servier. Prager G has received speaker honoraria from Servier, Merck Serono, MSD, BMS, Astra Zeneca, Lilly, Pierre Fabre, Bayer, Amgen, DaiichySankyo and Roche.

Authors' Contributions

Conception and design: Wöll E; Data analysis and interpretation: All Authors contributed equally; Manuscript writing: Wöll E, Prager G; 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", ZVR: 480557823, to Wöll E.

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Received April 5, 2023
Revised April 26, 2023
Accepted May 9, 2023