

Review

Chemotherapy in Gastric Cancer

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Abstract. *Although treatment of gastric cancer has improved substantially during the last decade there is still controversy about the best way and sequence of treatment. An early interdisciplinary treatment plan is mandatory before therapy is started. In this multidisciplinary expert statement we review current literature and give treatment recommendations for neoadjuvant, adjuvant, and palliative treatment of gastric cancer.*

Until the late 1990s surgical resection alone was the only accepted curative therapy option in gastric cancer. Chemotherapy (CT) and radiotherapy (RT) had relevance in the palliative setting only. This point of view has changed over recent years due to the development of new chemotherapeutic drugs and CT-regimens. The following recommendations of an Austrian expert committee reflect the state-of-the-art in Science and represent practical guidance for colleagues working in oncology. A principal distinction has to be made between the metastatic and adjuvant/neoadjuvant setting.

An overview of the different stages, the TNM-classification and its associated 5-year survival is shown in Table I.

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Metastatic and Locally Advanced Inoperable Gastric Cancer

Expert Recommendations

Indication. The clinical course of gastric cancer involves an immediate indication for therapy. “Watch and wait” is no treatment option for patients fit enough for CT. That therapy goal is a fast clinical response with the best possible quality of life. Based on phase-III studies a clear correlation between tumour response and an enhanced quality of life is assumed. If there is no clinical response, rapid staging needs to be conducted in order to exclude primary progression of the disease (*e.g.* in week 6-8). A lack of clinical and radiological response (after 3 cycles at the latest) should lead to a switch to a different treatment regimen.

In the case of stable disease with increased performance status and improved quality of life, the continuation of the first line therapy is indicated. These procedures follow the course of action of most phase-III-studies and reflect good clinical practice. In the case of asymptomatic patients a staging after half of the planned duration of therapy is standard. In patients in whom a response or disease stabilization has been achieved at manageable toxicity, the therapy should be continued.

Duration of treatment. Before starting the therapy, the therapeutic goal should be defined in an interdisciplinary way and determined together with the patient. Based on clinical experience, the therapy may be continued individually up to maximal response for responding patients who tolerate toxicity. In gastric cancer, this course of action is not yet based on prospective randomised trials.

Table I. Stages, TNM-classification and 5-year survival in gastric cancer.

Stage (%) ¹	TNM	5-year survival
0	TisN0M0	90
I	Ia: T1N0M0 Ib: T2N0M0 or T1N1M0	58-78
II	T1N2M0 or T2N1M0 or T3N0M0	34
III	IIIa: T2N2M0 or T3N1M0 or T4N0M0 IIIb: T3N2M0	8-20
IV	T1-3N3M0 or T4N1-3M0 or anyTanyNM1	7

Staging according to AJCC/UICC (33).

Medical treatment of locally advanced inoperable or metastatic gastric cancer. Meta-analyses have shown a clear advantage of CT over “best supportive care” (BSC) as well as an advantage of two agents compared to a monotherapy and of three agents compared to a chemotherapy combining two agents (1, 2). However, the data used in these meta-analyses partly resulted from very small trials using outdated staging methods, highly selected patient populations and different histologies and therefore are to be interpreted with caution.

Over the last decade many active substances have become available. 5-fluorouracil (5-FU), cisplatin, mitomycin C, etoposid, methotrexate and anthracyclin based chemotherapy regimens were used previously, whereas nowadays highly potent substances such as docetaxel, paclitaxel, capecitabine, oxaliplatin and irinotecan are available, all of them with proven efficacy in combination as first- and second-line therapy. Due to the possibility of an effective second-line treatment, the general course of treatment has changed such that in clinical practice a higher percentage of patients is treated with consecutive therapy. The use of antiangiogenic or epidermal growth factor receptor (EGFR)-targeting substances are experimental and not indicated outside clinical trials.

Based on phase-III-studies, a triple therapy, consisting of infusional 5-FU/capecitabine, cisplatin/oxaliplatin and docetaxel or an anthracyclin, has shown clear evidence of increased overall survival (OS) and of progression free survival (PFS) compared to a double or an older regimen (3,4). A direct comparison between these triple combination regimens (DCF = docetaxel, cisplatin 5-FU (page 6), ECF = epirubicin, cisplatin, 5-FU (page6)) is not available, but according to the results of the REAL-2-study, an equivalence of oxaliplatin with cisplatin and capecitabine with infusional 5-FU can be assumed (5,6).

One of these triple combinations should be used as the reference arm in future clinical trials.

In clinical practise, outside of clinical trials, the substantial bias concerning both the chemotherapy agent and the selection of patients should be considered when

interpreting trial results. This is relevant for the impairment of organs, existing co-morbidities and the performance status. In addition, no statements concerning the feasibility and distribution of second-line therapies, which could impact the results of individual treatment arms considerably, have been reported.

Based on these considerations, for first-line trials PFS is the more appropriate parameter than OS to evaluate different regimens. To meet all the requirements in respect to the whole patient-collective and to make use of successful second-line therapies, double chemotherapy, followed by effective regimens for progressive disease, could serve as a therapeutic concept at experienced centres, preferably within the frame of clinical trials.

Although the therapeutic value of, for example, docetaxel as a second-line regimen following non-taxane containing first-line combination regimens is well documented in phase II trials, such a sequence as a general schedule has not been tested. Randomised trials testing such protocols are not expected.

Palliative local therapy. Surgery/radiofrequency ablation/radiotherapy: Surgical resection of the primary tumour is not standard in a non-curative setting of locally advanced or metastatic gastric cancer. Depending on the clinical performance status and the severity of the symptoms (weight loss due to stenosis, pronounced bleeding, perforation, uncontrollable (intractable) pain, local palliative measures including radiotherapy or surgery should be considered.

Extended peritonectomies in combination with intraperitoneal CT +/- hyperthermia are extremely prone to complications, stressful and are not an element of standard procedure. Suitable local therapy can be considered in the case of local progression in otherwise stable disease.

Intraperitoneal therapy: Peritoneal carcinosis is a severe complication of advanced gastric carcinoma and represents a challenge for medical palliative care. So far, research on intraperitoneal therapies has been disappointing. The significance of antiangiogenic and other new therapeutic approaches is currently under evaluation.

Therapy of elderly patients. Age alone should not be an exclusion criterion for tumour-associated therapy. The few available studies have shown an equivalent response and consecutive improvement of performance status and quality of life in elderly as well as younger patients. However the increased therapy-associated toxicity should be considered. For the treatment of elderly patients, a high standard of patient education, leadership, communication and management of the most common co-morbidities and side-effects is necessary. An individually tailored therapy strategy should be designed based on these qualifications.

Supportive therapy. Since tumour-associated symptoms can reduce the performance status of patients significantly over a long period of time (stenosis, nutritional problems, depression), and since the dynamic of disease progression leaves only a short time for supportive therapy to take effect, supportive care is notably challenging in gastric cancer. Additionally, there is a frequent overlap between tumour-associated symptoms and therapy-associated side-effects, therefore, palliative medical expertise is of great importance in this situation.

Available Data

Tested combination regimen – response/efficacy/survival/toxicity. In phase-II studies in gastric cancer, combination-chemotherapy regimens have shown up to 65% higher response rates than monotherapy. However, these response rates could not be reached in randomised trials with the same regimens. The hazard-ratio favoured combination chemotherapy in terms of survival with 0.85 in a Cochrane-Review (1), although the survival benefit was only one month (median survival 7.0 vs. 5.9 months under monotherapy). Modern triple combinations (DCF, ECF) have shown an overall survival of 9 months (3, 4).

FAM. The FAM-regimen (5-FU, doxorubicin, mitomycin C) showed no superiority in a randomised study (7) over a 5-FU monotherapy and a combination of 5-FU and doxorubicin.

FAMTX. A direct comparison (8) between the FAMTX regimen (5-FU, doxorubicin, methotrexate) and the FAM regimen showed a significantly higher response rate (41% vs. 9%) and a significantly longer median survival (6.0 vs. 4.2 months) for FAMTX.

EAP. A trial (9) evaluating the EAP-regimen (etoposide, doxorubicin, cisplatin) against the FAMTX regimen, resulted in a 20% response rate in the EAP cohort compared with 33% in the FAMTX arm. No difference could be observed in the median survival. The EAP regimen increased the rate of lethal and toxic complications.

ELF and FUP. The ELF-regimen (etoposide, leucovorin, 5-FU), the FUP-regimen (5-FU, cisplatin) and the FAMTX regimen were compared in a phase III trial (10). None of the regimens showed a significant superiority in terms of response rate (9%, 20%, 12%), median survival (7.2 months, 7.2 months, 6.7 months) or toxicity.

ECF. The introduction of the ECF-regimen, consisting of epirubicin (50 mg/m² every 3 weeks), cisplatin (60 mg/m² every 3 weeks) and intravenous 5-FU (200 mg/m² daily), showed a definite improvement in results. In a randomised phase III trial (4) ECF showed superiority over FAMTX. The

response rate was significantly higher (45% vs. 21%) and the median survival increased significantly (8.9 vs. 5.7 months). Whereas there was more alopecia and nausea with the ECF treatment, FAMTX caused more haematological toxicities and infection. The necessity of a central venous access is a fundamental disadvantage of the ECF regimen. At least 15% of ECF treated patients showed complications directly related to the central venous access.

In previously untreated gastroesophageal carcinomas, ECF compared to a similar regimen, in which epirubicin was substituted with mitomycin (MCF; mitomycin 7 mg/m² every six weeks; cisplatin 60 mg/m² every 3 weeks; 5-FU 300 mg/m² daily) showed similar results concerning the response rate, survival and toxicities (11). Though the quality of life analysis favoured ECF. In the REAL-2 trial (5,6), ECF was compared to epirubicin/oxaliplatin/5-FU (EOF), epirubicin/cisplatin/capecitabine (ECX) or epirubicin/oxaliplatin/capecitabine (EOX) respectively in a 2x2 design. The study showed that neither oxaliplatin was inferior to cisplatin nor capecitabine to 5-FU. At 11.2 months, EOX showed a significantly better OS compared to ECF (9.9 months; $p=0.02$). The response rates and toxicities did not differ significantly. Thus it seems possible to substitute intravenous 5-FU by oral capecitabine. Patients treated with ECX showed a higher rate of grade 3 and 4 neutropenia compared to ECF (51.5% vs. 41.7%) whereas the rate of febrile neutropenia (FN) was not significantly different.

Docetaxel-based regimen. In the international phase III-study, “TAX 325” (3), the DCF regimen (21-day-cycles of docetaxel 75mg/m² on day1; cisplatin 75 mg/m² on day 1; continuous 5-FU 750 mg/m² on days 1 to 5) was compared to the CF regimen: 28 day cycles of cisplatin (100 mg/m² on day 1) and continuous 5-FU (1.000 mg/m² on days 1 to 5). The DCF treatment resulted in a significantly higher response rate (37% vs. 25%), a significantly longer time to progression (TTP; 5.6 vs. 3.7 months) and a higher 2-year survival (18% vs. 9%). This study led to the approval of Taxotere® in gastric cancer in the USA and Europe. DCF showed a higher incidence of G3/4 diarrhoea (20% vs. 8%) and in total, G3/4 toxicity occurred in 81% of the DCF and 75% of the CF patients.

According to the latest guidelines, the use of granulocyte-colony stimulating factors (G-CSF) is recommended if the primary rate of FN is higher than 20%. In the original study protocol of TAX325 this was not allowed, the patients who did not receive G-CSF showed a 28% FN-rate in the DCF arm whereas only 12% of patients who received secondary G-CSF experienced FN, a relative risk reduction of 57%. Other side-effects of the DCF-regimen are also predictable and manageable. The combination of docetaxel with capecitabine showed relatively consistent results in uncontrolled trials (12-15). Docetaxel was administered in dosages of either 75 mg/m² every 3-weeks or 36 mg/m²

every week and capecitabine was given in a dosage of 2x825 mg daily for the whole three week cycle or of 2x1.000 mg daily for the first two weeks. The response rates were between 39% and 44% , the median TTP between 4.2 and 5 months and the median overall survival between 8.4 and 12 months. Toxicity rates were generally low in these trials (10% neutropenia grade 3 and 4). Randomised studies and a direct comparison of this combination with the ECF-regimen, for example, are not available.

Irinotecan-based regimen. The combination of irinotecan (65 mg/m²) with weekly cisplatin (30 mg/m²), in 4 of 6 weeks showed an objective response rate of 58% and a median survival of 9 months in a small phase-II-trial (16). Toxicities included 27% G3/4 neutropenia, 3% “second cycle diarrhoea”, and 41% fatigue. No trial has compared this regimen to any other chemotherapy regimen in gastric cancer, nor have any randomised phase III trials been conducted.

A French phase II trial (17) showed superiority of the FOLFIRI-regimen (continuous 5-FU, leucovorin, irinotecan, originally developed for colorectal cancer) over leucovorin/5-FU with or without cisplatin. Also, for an irinotecan/ oxaliplatin combination, an Austrian phase II trial (18) showed a median survival of more than 9 months at low toxicity rates. However, these combinations have not been tested in randomized trials.

Oxaliplatin-based regimen. The REAL-2 study has already been described under ECF. An additional phase III study (19) compared the FLO-regimen (continuous 5-FU 2.600 mg/m² over 24 h; leucovorin 200 mg/m²; oxaliplatin 85 mg/m²; every two weeks) to the FLP regimen (continuous 5-FU 2.000 mg/m² over 24 h; leucovorin 200 mg/m² weekly; cisplatin 50 mg/m² every two weeks). Concerning the response rate (34 vs. 25%) and the TTP (5.7 vs. 3.8 months), no significant difference could be observed. The FLO regimen was associated with significantly less nausea, vomiting, fatigue, renal toxicity and alopecia, but more grade 3/4 sensory neuropathy.

Elderly patients. In advanced gastric cancer trials, elderly patients are underrepresented. Monotherapy (e.g. 5-FU (plus leucovorin)) is a therapy option for elderly patients and patients with a low performance status and other monotherapies (e.g. capecitabine, irinotecan and others) could also be used. The “TAX 325” study (3) showed that a docetaxel-based combination regimen like DCF could be used in selected elderly patients, since 24% of the study cohort were older than 65 years. Subgroup analyses were performed in terms of TTP and OS. For both TTP and OS there was no appreciable difference in a comparison of patients older and younger than 65 years. In all the clinical parameters the DCF regimen was superior to the CF regimen.

Quality of life. The importance of quality of life in oncology has become more prominent in recent years, which was not much emphasised in earlier research. Only few data are available about the impact of combination-chemotherapy-regimens on the quality of life of patients with advanced gastric cancer.

A study published in 1997 (2), comparing best supportive care to CT, resulted in a better median survival for chemotherapy compared to best supportive care, even when taking the quality of life effects into account.

In two studies (4, 11) the ECF regimen was compared to FAMTX and MCF, and showed a higher quality of life benefit. These findings were limited though by the fact that the patients enrolled were quite young in age and were not representative of the average patients with advanced gastric cancer seen in clinical practice. In particular patients with comorbidities such as kidney or heart diseases were excluded.

The TAX325 trial (3) showed that DCF compared to CF resulted in a higher quality of life. Among other parameters, the time to 5% worsening of global health status (GHS) was measured. A time to worsening of the GHS of 6.5 months in DCF compared to 4.2 months in the CF arm respectively represent a 30.8% relative risk reduction and a significant difference favouring DCF. With the exception of cancer pain, all parameters measuring quality of life favoured DCF compared to CF.

In a smaller trial DCF and ECF were compared concerning health related quality of life (20). With equal baseline parameters, only the DCF-arm showed a statistically significant and clinically relevant improvement in overall quality of life.

Future therapy options. A series of trials using different combinations (e.g. docetaxel plus imatinib; Docetaxel plus bevacizumab and many more) are ongoing.

In a phase II trial (21), the combination of cisplatin and irinotecan with the vascular endothelial growth factor (VEGF)-antibody bevacizumab showed a high response rate in 33 patients and a median survival of 12.3 months, albeit that toxicity was substantial.

A combination of the EGFR-antibody cetuximab with FOLFIRI showed a response rate of 56% at a relatively high neutropenia rate (22).

Adjuvant/Neoadjuvant/Perioperative Therapy of Gastric Cancer

Expert Recommendations

Indication. An interdisciplinary tumour board prior to any therapeutic treatment is mandatory based on the current available therapeutic options.

Staging. As the primary diagnostic method an endoscopy plus biopsy must be performed.

Table II. *Therapeutic treatments based on the T-stage*

T-stage	Therapy option
1-4	Adequate resection at a centre experienced in multimodal therapeutic treatment
≥2	<p>Evaluate perioperative (<i>i.e.</i> pre- and postoperative chemotherapy)</p> <p>In the hitherto available phase-III trials, chemotherapy was performed up to 12 weeks pre- and post surgery.</p> <p>If perioperative chemotherapy was not considered initially and patients present after primary resection and simultaneously with less than 15 histopathologically examined lymph nodes, a postoperative radio-chemo-therapy should be considered.</p> <p>This also holds true for patients in a critical nutritional condition and with potentially resectable tumours, and for whom a delay of surgery may lead to an unfavourable course of disease</p>

If the tumour represents an early carcinoma in endoscopic diagnosis and if a limited resection is an option, an endosonography should be performed.

A computer tomography thorax/abdomen/pelvis (spiral-CT, *i.v.* contrast agent plus an oral, negative contrast agent) is mandatory for preoperative staging. An abdomen-sonography can be performed additionally. If the tumour stage is not clearly <cT2, an endosonography may be of additional value in order to exclude the infiltration of neighbouring structures.

Additional staging methods depend on the individual situation and the symptoms the patients are presenting with. They may for example include a more detailed examination of liver, bones and brain.

In clinical stages beyond cT2, a laparoscopic exploration should be performed in cases of a curative therapeutic possibility.

Curative treatment. Table II shows the currently available therapeutic options sorted by T-stage of the tumour.

Specific therapeutic regimen. Until new data is available from fully published reports, the ECF-regimen used in the MAGIC-trial (23) should be used for perioperative CT. Combined radio-chemotherapy should be used according to the scheme evaluated in the Intergroup 0116-trial for adjuvant treatment (24). Further possibilities of combination therapies serving to increase efficacy and/or reduce toxicity, should only be used within the frame of prospective trials.

An adequate, continuous supportive therapy and increased vigilance towards therapy-associated complications are a necessity.

Available Data

Perioperative therapy. In the MAGIC-trial (23) patients were treated with 3 pre- and 3 postoperative chemotherapy cycles using the ECF-regimen.

The control group underwent surgery without CT. Seventy nine % of patients in the perioperative arm *vs.* 70% in the control arm had potentially curative surgery, and significantly more patients (52% *vs.* 37%) had T1/2-tumours or N0/1-disease (84 *vs.* 71%), respectively. After 4 years, the relative PFS in the surgery-only group was 34% lower and the relative OS was 25% lower compared to the perioperative therapy regimen. The 5-year survival rate increased from 23% to 36% with perioperative therapy.

Neoadjuvant therapy. The FNLCC 94012 (ACCORD07) (24) was an additional phase-III trial presented at the ASCO 2007. Patients with resectable carcinoma of the stomach and the distal esophagus were treated either with a preoperative chemotherapy including infusional 5-FU and cisplatin (FP) followed by surgery or surgery alone. CT significantly increased the rate of R0-resections from 73% to 84%. Preoperative chemotherapy improved DFS ($p=0.003$) with 3 and 5-year DFS of 25% and 21% *vs.*

Table III. *Available data concerning adjuvant chemotherapy in gastric cancer.*

Trial	Patient number	Conclusion
Hermans J <i>et al.</i> (25)	>2.000 11(13) trials	Only a marginal survival benefit
Earle CC <i>et al.</i> (26)	13 trials	Borderline significant survival benefit
Mari E <i>et al.</i> (27)	3.658 20 trials, 1965-1999	Advantage in stage I and II 3%, Advantage in stage III 5%
Panzini I <i>et al.</i> (28)	3.118 17 trials	Small survival benefit
Cascinu S <i>et al.</i> (29)	397 phase II	No survival benefit (cisplatin, epirubicin, leucovorin, 5-FU)
Macdonald JS <i>et al.</i> (30)	556 phase III (Chemoradiation)	Significant survival benefit with adjuvant radio-chemotherapy
Sakamoto J <i>et al.</i> (31)	1.503 4 trials	Significant survival benefit (tegafur/uracil)
Sasako M <i>et al.</i> (32)	1.059 phase-III-trial	Significant OS and PFS benefit (S-I*)

*Tegafur/Gimeracil/Oteracil.

40% and 34%, respectively. The 3 and 5 year OS increased from 35% and 24% up to 48% and 38% upon preoperative chemotherapy.

Adjuvant therapy. Table III summarizes the relevant meta-analyses and trials dealing with adjuvant chemotherapy in gastric cancer.

In general, the available data do not favour the use of adjuvant (postoperative) CT (difficult to administer, feasible in a rather small number of patients only). The majority of randomised single trials generated negative or inconclusive results. In big meta-analyses only a marginal effect of adjuvant CT could be observed.

From the current point of view, adjuvant CT in gastric cancer can be used in individual cases, but does not represent a therapeutic standard.

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