REVIEW

Lib Oncol. 2021;49(2-3):103–107

doi: 10.20471/LO.2021.49.02-03.14

PERIOPERATIVE TREATMENT OF GASTRIC CANCER - SHORT REVIEW

JOSIPA FLAM[1,2], LUKA PERIĆ[1,2], MIRELA ŠAMBIĆ PENC[1,2], MAJA KOVAČ BARIĆ[1], DARKO KOTROMANOVIĆ[1,2], NORA PUŠELJIĆ[2,3] and IVANA CANJKO[1]

[1]Department of Oncology, University Hospital Center Osijek, Osijek, Croatia;
[2]Faculty of Medicine, University of J.J.Strossmayer Osijek, Osijek, Croatia;
[3]Emergency medicine, University Hospital Center Osijek, Osijek, Croatia

Summary

Adenocarcinoma of the gastroesophageal junction (GEJ) and gastric cancer have poor outcomes in most patients.

Perioperative chemotherapy became a standard of care for resectable adenocarcinoma of the upper GI tract based on the results of the MAGIC trial. The study includes patients with Stage II or III resectable adenocarcinoma of the stomach, GEJ, and lower esophagus. The ACCORD trial essentially supported the results of the MAGIC study.

Both studies showed that preoperative chemotherapy could induce downstaging and enhance the possibility of potentially curative R0 resection, thus increasing the probability of disease-free survival and overall survival.

The NeoFLOT study investigates the application of prolonged neoadjuvant chemotherapy (NACT). This study indicates that NACT with six cycles of FLOT is highly effective in resectable gastroesophageal cancer. The CRITICS trial compares perioperative chemotherapy with preoperative and postoperative chemoradiotherapy in patients with resectable gastric adenocarcinoma. Postoperative chemoradiotherapy did not improve overall survival compared with postoperative chemotherapy in patients with resectable gastric cancer treated with adequate preoperative chemotherapy and surgery.

In recent years, guidelines for the treatment of gastric cancer have changed frequently. Because gastric cancer treatment is complex and perioperative chemotherapy is present in all treatment guidelines, a multidisciplinary team with experienced physicians is the foundation of effective gastric cancer treatment.

KEYWORDS: *stomach neoplasms, chemoradiotherapy, neoadjuvant chemotherapy*

INTRODUCTION

Adenocarcinoma of the gastroesophageal junction (GEJ) and gastric cancer has poor outcomes in most patients.

Gastric cancer has over one million new cases in one year, and because of that, it is globally non-neglectable. With over one million cases annually, it is the fifth most diagnosed neoplasm in the world. Because of its poor overall survival and extreme aggressiveness, it is globally ranked fourth for mortality in 2020(1,2). Because of late diagnosis, the prognosis is very poor, with an average 5-year survival rate of less than 20%. Countries like Japan have set up screening programs that help with early detection. If cancer is detected and treated before invading the muscular layer, the 5-year survival rate is exceptionally high and can reach up to 90%(3). The tumor stage is the most important factor determining the treatment modality, treatment effectiveness, and strategy. Early gastric cancer can undergo radical operation followed by chemotherapy, and its 5-year survival

***Corresponding author**: Josipa Flam, Department of Oncology, University Hospital Center Osijek, J.Huttlera 4, 31000 Osijek and Faculty of Medicine, University of J.J.Strossmayer Osijek, Cara Hadrijana 10E, 31000 Osijek, Croatia. e-mail jflam@mefos.hr*

rate can be high as 90%. On the other hand, most patients will develop the advanced-stage disease because of low detection rates and lack of symptoms, and their prognosis is poor(4).

MODALITY OF THE THERAPY

The combined modality therapy significantly increases survival in patients with locoregional gastric cancer(5-7). The most common approach for localized resectable disease (≥cT2 and/or N+) is perioperative chemotherapy. If the patients receive less than D2 lymph node dissection, the choice is postoperative chemoradiation(6,8-11). Other treatment options include preoperative chemoradiation or postoperative chemotherapy (12-14).

RADIATION THERAPY (RT)

Radiation therapy (RT) is applied both preoperatively and postoperatively in patients with resectable gastric cancer. RT used as a single modality treatment option has minimal value in patients with unresectable gastric cancer(15). However, several studies showed that if RT is used concurrently with chemotherapy, it can significantly improve survival. In one study comparing a group that used fluorouracil plus RT with a group that used RT alone to treat locally advanced unresectable gastric cancer(16), patients receiving combined modality treatment had significantly better median survival (13 months vs. 6 months) and 5-year OS (12% vs. 0%) rates.

A multicenter phase III randomized CROSS trial showed that preoperative chemoradiation with paclitaxel and carboplatin significantly improved OS and DFS compared to surgery alone in patients with resectable (T2–3, N0–1, M0) esophageal or EGJ cancers(13).

A postoperative chemoradiation therapy trial, INT-0116, investigated the effectiveness of surgery followed by postoperative chemotherapy plus chemoradiation on the survival of patients with resectable gastric or EGJ adenocarcinoma (17,18). INT-0116 trial patients (stage IB to IV, M0) who had not received preoperative therapy were randomized to receive surgery followed by postoperative chemotherapy plus chemoradiation or surgery alone(17). After a median follow-up of 5 years, the median OS in the surgery-only group was 27 months compared to 36 months in the postoperative chemotherapy plus chemoradiation group. Also, the postoperative chemotherapy plus chemoradiation group had better 3-year OS (50% vs. 41%) and RFS rates (48% vs. 31%) than the group that underwent surgery alone.

PERIOPERATIVE CHEMOTHERAPY

Perioperative chemotherapy became a standard of care for resectable adenocarcinoma of the upper GI tract in most Western European countries based on the results of the MAGIC trial, and it was tested in several Asian trials. Including patients with Stage II or III resectable adenocarcinoma of the stomach, GEJ, and lower esophagus, these studies demonstrated the benefit from chemotherapy with three cycles of the ECF regimen (epirubicin, cisplatin, 5-fluorouracil) applied before and after surgery as compared to surgery alone. The results of the MAGIC study were essentially supported by the French ACCORD trial. In the ACCORD trial, there was a significantly higher R0 resection rate and a non-significant decrease in lymph node metastasis in the group of patients that received perioperative chemotherapy with fluorouracil and cisplatin(9,11). Both studies showed that preoperative chemotherapy could induce downstaging and enhance the possibility of potentially curative R0 resection, thus increasing the probability of disease-free survival and overall survival.

The next step in perioperative chemotherapy was the addition of docetaxel. The combination of docetaxel, cisplatin, and 5-fluorouracil (DCF) improved efficacy in gastric cancer but was associated with substantial toxicity. This multicenter study from 2016 compared DCF regimen as perioperative chemotherapy with patients that underwent surgery alone. The study results showed that perioperative DCF chemotherapy is superior to surgery alone in overall survival (OS)(19).

Between August 8. 2010, and February 10. 2015, 716 patients were randomly assigned to treatment in 38 German hospitals or with practice-based oncologists. Three hundred sixty patients received epirubicin, cisplatin, and 5-fluorouracil/capecitabine (ECF/ECX), and 356 patients received 5-fluorouracil plus leucovorin, oxaliplatin, and

docetaxel (FLOT). In the FLOT group, patients received four cycles of chemotherapy before and four cycles after surgery.

The study showed that median OS increased in the FLOT group compared with the ECF group (50 months vs. 35 months; HR = 0.77; 95% CI, 0.63–0.94). Also, the percentage of patients with chemotherapy-related severe adverse events was the same in the two groups (27% in the ECF group vs. 27% in the FLOT group). Because of the following study results, ECF should no longer be recommended in this setting. On the other hand, the panel recommends its use in patients with good performance status because of considerable toxicity recorded with the FLOT regimen. For good to moderate performance patients, the status regimen of choice is fluorouracil and oxaliplatin (FOLFOX)(8). Nevertheless, only half of the patients can receive adjuvant chemotherapy, which might imply that the great benefit of perioperative chemotherapy is due to the preoperative part of treatment alone(7).

The NeoFLOT-study, therefore, investigates the application of prolonged neoadjuvant chemotherapy (NACT). Patients with T3, T4, and/or node-positive adenocarcinoma were eligible for this multicenter phase II trial. NACT consisted of 6 cycles of oxaliplatin 85 mg/m2, leucovorin 200 mg/m2, 5-fluorouracil 2600 mg/m2 and docetaxel 50 mg/m2 (FLOT) every 2 weeks without adjuvant chemotherapy. The primary endpoint was the R0-resection rate. This study indicates that intensified NACT with six cycles of FLOT is highly effective and tolerable in resectable GEC, especially in intestinal type of tumor(20).

The CRITICS trial compared perioperative chemotherapy with preoperative chemotherapy and postoperative chemoradiotherapy in patients with resectable gastric adenocarcinoma. Postoperative chemoradiotherapy did not improve overall survival compared with postoperative chemotherapy in patients with resectable gastric cancer treated with adequate preoperative chemotherapy and surgery. A possible explanation is the poor postoperative compliance in both groups, so we need further trials(10).

Japan differs from Western countries in the treatment of locally advanced gastric cancer. The standard treatment in Japan for this kind of disease is surgery with postoperative adjuvant chemotherapy. However, patients with gastric cancer with extensive lymph node metastasis have poor survival outcomes with preoperative neoadjuvant chemotherapy. A multicenter randomized controlled trial named JCOG0501 aims to demonstrate the efficacy of preoperative neoadjuvant chemotherapy with S-1 plus cisplatin for patients with type 4 or large type gastric cancer(21). Patients were randomized to gastrectomy plus adjuvant chemotherapy with S-1 or NAC followed by gastrectomy + adjuvant chemotherapy. Statistical analysis showed that survival outcomes were pretty similar in the two groups. 3-year relapse-free survival (RFS) rates of 60.9% and 62.4% for patients who received preoperative neoadjuvant chemotherapy versus those who did not, respectively (hazard ratio, 0.916; 95% CI, 0.679–1.236)(22).

CLASSIC trial in Korea showed 3-year disease-free survival of 74% when surgery was followed by chemotherapy and 59% in the surgery alone group, with a hazard ratio of 0.56 (95% CI, 0.44–0.72). After the CLASSIC trial, postoperative adjuvant chemotherapy with capecitabine plus oxaliplatin became a standard for locally advanced gastric cancer(23,24).

ARTIST trial showed the efficacy of adjuvant chemoradiotherapy following D2 gastrectomy. In this trial, patients undergoing curative resection were assigned either in an adjuvant chemotherapy group or an adjuvant chemoradiotherapy group. The results showed that survival was slightly better in the chemoradiotherapy group, but the difference was not significant (78.2% vs. 74.2%, p = 0.0862). Nevertheless, subset analysis showed the potential benefit of adjuvant chemoradiotherapy in node-positive locally advanced gastric cancer(25). Also, results of the ARTIST 2 trial showed that in patients with curatively D2-resected, stage II/III, node-positive GC, adjuvant S-1 plus oxaliplatin (SOX), and S-1 plus oxaliplatin with chemoradiotherapy (SOXRT) was effective in prolonging DFS, when compared with S-1 monotherapy(26).

The final results of the new PRODIGY trial (NCT01515748) in Korea are imminent, and they will show the results of preoperative neoadjuvant chemotherapy with docetaxel, oxaliplatin, and S-1(27).

According to this, perioperative chemotherapy is incorporated in all guidelines for the treatment of gastric cancer. Because gastric cancer treatment is complex and perioperative chemo-

therapy is present in all treatment guidelines, all patients should be treated in centers with a good multidisciplinary approach and experience in treating these patients.

REFERENCES

1. Cuschieri A, Weeden S, Fielding J, Bancewicz J, Craven J, Joypaul V, et al. Patient survival after D1 and D2 resections for gastric cancer: long-term results of the MRC randomized surgical trial. Surgical Co-operative Group. Br J Cancer. 1999;79(9-10):1522-30.
2. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. CA Cancer J Clin. 2021;71(3):209-49.
3. Miyahara R, Niwa Y, Matsuura T, Maeda O, Ando T, Ohmiya N, et al. Prevalence and prognosis of gastric cancer detected by screening in a large Japanese population: data from a single institute over 30 years. J Gastroenterol Hepatol. 2007;22(9):1435-42.
4. Song Z, Wu Y, Yang J, Yang D, Fang X. Progress in the treatment of advanced gastric cancer. Tumour Biol. 2017;39(7):1010428317714626.
5. Al-Batran SE, Lorenzen S. Management of Locally Advanced Gastroesophageal Cancer: Still a Multidisciplinary Global Challenge? Hematol Oncol Clin North Am. 2017;31(3):441-52.
6. Cai Z, Yin Y, Shen C, Wang J, Yin X, Chen Z, et al. Comparative effectiveness of preoperative, postoperative and perioperative treatments for resectable gastric cancer: A network meta-analysis of the literature from the past 20 years. Surg Oncol. 2018;27(3):563-74.
7. Coccolini F, Nardi M, Montori G, Ceresoli M, Celotti A, Cascinu S, et al. Neoadjuvant chemotherapy in advanced gastric and esophago-gastric cancer. Meta-analysis of randomized trials. Int J Surg. 2018;51:120-7.
8. Al-Batran SE, Homann N, Pauligk C, Goetze TO, Meiler J, Kasper S, et al. Perioperative chemotherapy with fluorouracil plus leucovorin, oxaliplatin, and docetaxel versus fluorouracil or capecitabine plus cisplatin and epirubicin for locally advanced, resectable gastric or gastro-oesophageal junction adenocarcinoma (FLOT4): a randomised, phase 2/3 trial. Lancet. 2019; 393(10184):1948-57.
9. Ychou M, Boige V, Pignon JP, Conroy T, Bouché O, Lebreton G, et al. Perioperative chemotherapy compared with surgery alone for resectable gastroesophageal adenocarcinoma: an FNCLCC and FFCD multicenter phase III trial. J Clin Oncol. 2011;29(13):1715-21.
10. Cats A, Jansen EPM, van Grieken NCT, Sikorska K, Lind P, Nordsmark M, et al. chemotherapy versus chemoradiotherapy after surgery and preoperative chemotherapy for resectable gastric cancer (CRITICS): an international, open-label, randomised phase 3 trial. Lancet Oncol. 2018;19(5):616-28.
11. Cunningham D, Allum WH, Stenning SP, Thompson JN, Van de Velde CJ, Nicolson M, et al. Perioperative chemotherapy versus surgery alone for resectable gastroesophageal cancer. N Engl J Med. 2006;355(1):11-20.
12. Ajani JA, Winter K, Okawara GS, Donohue JH, Pisters PW, Crane CH, et al. Phase II trial of preoperative chemoradiation in patients with localized gastric adenocarcinoma (RTOG 9904): quality of combined modality therapy and pathologic response. J Clin Oncol. 2006;24(24):3953-8.
13. van Hagen P, Hulshof MC, van Lanschot JJ, Steyerberg EW, van Berge Henegouwen MI, Wijnhoven BP, et al. Preoperative chemoradiotherapy for esophageal or junctional cancer. N Engl J Med. 2012;366(22):2074-84.
14. Shapiro J, van Lanschot JJB, Hulshof M, van Hagen P, van Berge Henegouwen MI, Wijnhoven BPL, et al. Neoadjuvant chemoradiotherapy plus surgery versus surgery alone for oesophageal or junctional cancer (CROSS): long-term results of a randomised controlled trial. Lancet Oncol. 2015;16(9):1090-8.
15. Hazard L, O'Connor J, Scaife C. Role of radiation therapy in gastric adenocarcinoma. World J Gastroenterol. 2006;12(10):1511-20.
16. Moertel CG, Childs DS, Jr., Reitemeier RJ, Colby MY, Jr., Holbrook MA. Combined 5-fluorouracil and supervoltage radiation therapy of locally unresectable gastrointestinal cancer. Lancet. 1969;2(7626):865-7.
17. Macdonald JS, Smalley SR, Benedetti J, Hundahl SA, Estes NC, Stemmermann GN, et al. chemoradiotherapy after surgery compared with surgery alone for adenocarcinoma of the stomach or gastroesophageal junction. N Engl J Med. 2001;345(10):725-30.
18. Smalley SR, Benedetti JK, Haller DG, Hundahl SA, Estes NC, Ajani JA, et al. Updated analysis of SWOG-directed intergroup study 0116: a phase III trial of adjuvant radiochemotherapy versus observation after curative gastric cancer resection. J Clin Oncol. 2012; 30(19):2327-33.
19. Fiteni F, Paget-Bailly S, Messager M, N'Guyen T, Lakkis Z, Mathieu P, et al. Docetaxel, Cisplatin, and 5-Fluorouracil as perioperative chemotherapy compared with surgery alone for resectable gastroesophageal adenocarcinoma. Cancer Med. 2016;5(11):3085-93.
20. Schulz C, Kullmann F, Kunzmann V, Fuchs M, Geissler M, Vehling-Kaiser U, et al. NeoFLOT: Multicenter phase II study of perioperative chemotherapy in resectable adenocarcinoma of the gastroesophageal junction or gastric adenocarcinoma-Very good response predominantly in patients with intestinal type tumors. Int J Cancer. 2015;137(3):678-85.
21. Terashima M, Iwasaki Y, Mizusawa J, Katayama H, Nakamura K, Katai H, et al. Randomized phase III trial of gastrectomy with or without neoadjuvant S-1 plus cisplatin for type 4 or large type 3 gastric cancer, the short-term safety and surgical results: Japan Clinical Oncology Group Study (JCOG0501). Gastric Cancer. 2019;22(5):1044-52.

22. Iwasaki Y, Terashima M, Mizusawa J, Katayama H, Nakamura K, Katai H, et al. gastrectomy with or without neoadjuvant S-1 plus cisplatin for type 4 or large type 3 gastric cancer (JCOG0501): an open-label, phase 3, randomized controlled trial. Gastric Cancer. 2021; 24(2):492-502.
23. Bang YJ, Kim YW, Yang HK, Chung HC, Park YK, Lee KH, et al. Adjuvant capecitabine and oxaliplatin for gastric cancer after D2 gastrectomy (CLASSIC): a phase 3 open-label, randomised controlled trial. Lancet. 2012;379(9813):315-21.
24. Noh SH, Park SR, Yang HK, Chung HC, Chung IJ, Kim SW, et al. Adjuvant capecitabine plus oxaliplatin for gastric cancer after D2 gastrectomy (CLASSIC): 5-year follow-up of an open-label, randomised phase 3 trial. Lancet Oncol. 2014;15(12):1389-96.
25. Lee J, Lim DH, Kim S, Park SH, Park JO, Park YS, et al. Phase III trial comparing capecitabine plus cisplatin versus capecitabine plus cisplatin with concurrent capecitabine radiotherapy in completely resected gastric cancer with D2 lymph node dissection: the ARTIST trial. J Clin Oncol. 2012;30(3):268-73.
26. Park SH, Lim DH, Sohn TS, Lee J, Zang DY, Kim ST, et al. A randomized phase III trial comparing adjuvant single-agent S1, S-1 with oxaliplatin, and postoperative chemoradiation with S-1 and oxaliplatin in patients with node-positive gastric cancer after D2 resection: the ARTIST 2 trial. Ann Oncol. 2021;32(3):368-74.
27. Tokunaga M, Sato Y, Nakagawa M, Aburatani T, Matsuyama T, Nakajima Y, et al. Perioperative chemotherapy for locally advanced gastric cancer in Japan: current and future perspectives. Surg Today. 2020;50 (1):30-7.

Sažetak

PERIOPERATIVNO LIJEČENJE KARCINOMA ŽELUCA - KRATAK PREGLED

J. Flam, L. Perić, M. Šambić Penc, I. Canjko, M. Kovač Barić, D. Kotromanović, N. Pušeljić

Adenokarcinom gastroezofagealnog prijelaza (GEJ) i karcinom želuca bolest je koja je kod većine bolesnika povezana s lošim ishodom.

Perioperativna kemoterapija postala je standard liječenja za resektabilni adenokarcinom gornjeg dijela GI trakta na temelju rezultata ispitivanja MAGIC studije. Studija uključuje bolesnike s II ili III stadijem resektabilnog adenokarcinoma želuca, GEJ-a i donjeg dijela jednjaka. Rezultati studije MAGIC u osnovi su podržani ispitivanjima ACCORD.

Sumirajući, obje studije pokazale su da preoperativna (neoadjuvantna) kemoterapija može izazvati smanjenje veličine tumora i povećati mogućnost potencijalne R0 resekcije, povećavajući tako vjerojatnost preživljavanja bez bolesti i ukupnog preživljavanja.

Studija NeoFLOT istražuje primjenu produljene neoadjuvantne kemoterapije (NACT). Ova studija pokazuje da je NACT sa 6 ciklusa FLOT-a vrlo učinkovita kod resektabilnog gastroezofagealnog karcinoma.

Ispitivanje CRITICS uspoređuje perioperativnu kemoterapiju s preoperativnom i postoperativnom kemoradioterapijom u bolesnika s resektabilnim adenokarcinomom želuca. Postoperativna kemoradioterapija nije poboljšala ukupno preživljenje u usporedbi s postoperativnom kemoterapijom u bolesnika s resektabilnim karcinomom želuca koji su liječeni odgovarajućom predoperativnom kemoterapijom i operativnim zahvatom.

Posljednjih godina često se mijenjaju smjernice za liječenje karcinoma želuca. Iz razloga što je liječenje karcinoma želuca kompleksno i perioperativna kemoterapija je prisutna u svim smjernicama za liječenje, multidisciplinarni tim s iskusnim liječnicima temelj je učinkovitog liječenja karcinoma želuca.

KLJUČNE RIJEČI: *novotvorine želuca, kemoradioterapija, neoadjuvantna kemoterapija*