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Novel Therapies in the Perioperative Management of Localized Gastric Cancer: Current Perspectives and Future Directions

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Abstract: The management of localized gastric cancer has evolved considerably with the advent of novel perioperative treatment strategies with chemotherapy, significantly impacting patient outcomes. Traditionally, surgery has been the cornerstone of treatment, but recurrence rates remained high, necessitating the exploration of additional therapies to enhance long-term survival. The interplay between chemotherapy and radiotherapy is being meticulously studied to define the optimal sequencing and combination that maximizes tumor control while minimizing toxicity. Furthermore, the integration of targeted therapies and immunotherapy into the perioperative setting is gaining momentum with agents targeting HER2, VEGF, and PD-1/PD-L1, pathways have shown promise in advanced gastric cancer and are now being tested in the neoadjuvant and adjuvant settings. Preliminary results from trials investigating these agents, such as pembrolizumab and trastuzumab-deruxtecan, suggest potential survival benefits and warrant further exploration in combination with chemotherapy in the perioperative context. Additionally, the heterogeneity of gastric cancer across different populations and geographic regions necessitates tailored approaches that consider genetic and molecular characteristics of tumors, as well as patient comorbidities. This Comment provides a comprehensive overview of the latest therapeutic advancements in the perioperative setting for localized gastric cancer, emphasizing the critical role of multimodal treatment approaches.

Keywords: Gastric cancer; novel therapies; cancer treatment.

Novas Terapias no Tratamento Perioperatório do Câncer Gástrico Localizado: Perspectivas Atuais e Direções Futuras

Resumo: O tratamento do câncer gástrico localizado evoluiu consideravelmente com o advento de novas estratégias de tratamento perioperatório com quimioterapia, impactando significativamente os resultados dos pacientes. Tradicionalmente, a cirurgia tem sido a pedra angular do tratamento, mas as taxas de recorrência permaneceram altas, necessitando da exploração de terapias adicionais para aumentar a sobrevida a longo prazo. A interação entre quimioterapia e radioterapia está sendo meticulosamente estudada para definir o sequenciamento e a combinação ideais que maximizam o controle do tumor, minimizando a toxicidade. Além disso, a integração de terapias direcionadas e imunoterapia no ambiente perioperatório está ganhando força com agentes que visam HER2, VEGF e PD-1/PD-L1, vias que se

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mostraram promissoras no câncer gástrico avançado e agora estão sendo testadas nos ambientes neoadjuvante e adjuvante. Resultados preliminares de ensaios que investigam esses agentes, como pembrolizumabe e trastuzumabe-deruxtecano, sugerem potenciais benefícios de sobrevivência e garantem maior exploração em combinação com quimioterapia no contexto perioperatório. Além disso, a heterogeneidade do câncer gástrico em diferentes populações e regiões geográficas necessita de abordagens personalizadas que considerem características genéticas e moleculares dos tumores, bem como comorbidades do paciente. Este Comentário fornece uma visão geral abrangente dos últimos avanços terapêuticos no cenário perioperatório para câncer gástrico localizado, destacando o papel crítico das abordagens de tratamento multimodal.

Palavras-chave: Câncer gástrico; novas terapias; tratamento do câncer.

Introdução

The concept of perioperative chemotherapy has emerged as a critical advancement in the management of localized gastric cancer.[1,15] Several landmark trials, including the MAGIC (Medical Research Council Adjuvant Gastric Infusional Chemotherapy) and FLOT4 trials, have established the efficacy of this approach.[1,3] The MAGIC trial, which compared perioperative chemotherapy using ECF (epirubicin, cisplatin, and 5-fluorouracil) with surgery alone, demonstrated a significant improvement in overall survival (OS) and progression-free survival (PFS), setting the stage for the integration of chemotherapy into the perioperative period.[2]

For patients with clinical stage cT2-4 or cN+M0, perioperative treatment with the chemotherapy regimen based on the FLOT4 Study (docetaxel, 50 mg/m² IV, on D1; 5-FU, 2,600 mg/m² IV, over 24 h, on D1; DL-leucovorin, 200 mg/m² IV, on D1; and oxaliplatin, 85 mg/m² IV, on D1) is recommended. This regimen is administered every 14 days, with 4 cycles neoadjuvantly, followed by surgical resection and an additional 4 cycles of adjuvant chemotherapy.[1]

With a median follow-up of 43 months, the FLOT regimen resulted in increased OS (median 35 versus 50 months, HR=0.77; 95% CI: 0.63-0.94; p=0.012), PFS (median 18 versus 30 months, HR=0.75; 95% CI: 0.62-0.91; p=0.004), and pathological complete response (pCR) (16% versus 6%; p=0.02).1 Perioperative toxicity was similar in both arms: 50% with ECF/ECX and 51% with FLOT. However, more cases of grade 3 and 4 nausea and vomiting were observed with ECF/ECX, while more cases of grade 3 and 4 neutropenia were observed with FLOT.[1]

Consequently, this regimen has become the new standard for perioperative chemotherapy in gastric cancer.[1]

Despite these advancements, several questions remain. The toxicity associated with the FLOT regimen, particularly in older or frail patients, raises concerns about its broad applicability.1 Tailoring treatment to individual patient characteristics, including age, comorbidities, and tumor biology, is essential to optimize outcomes while minimizing adverse effects.1 Further research is needed to refine patient selection criteria and explore potential biomarkers that may predict response to perioperative chemotherapy.1 Secondary options for patients who are not candidates for the FLOT regimen include 5-FU and platinum-based regimens, such as FOLFOX (5-FU, leucovorin, and oxaliplatin).[1]

The MAGIC study randomized 503 patients with operable adenocarcinoma of the stomach (74%), distal esophagus (15%), and esophagogastric junction (11%) to ECF for 3 preoperative cycles followed by surgery, then 3 postoperative cycles (90.7% received all preoperative chemotherapy, but only 41.6% of individuals received the planned postoperative chemotherapy), versus surgery alone (control arm).[2] There was no difference in surgical morbidity between the two arms (45.7% versus 45.3%), but there was a higher incidence of curative surgery (79.3% versus 70.3%; p=0.003) and of T1 and T2 tumors (51.7% versus 36.8%; p=0.002) in patients treated with chemotherapy. With a median follow-up of 4 years, an increase in PFS (HR=0.66; 95% CI: 0.53-0.81; p<0.001) and OS (HR=0.75; 95% CI: 0.6-0.93; p=0.009) was observed in favor of the chemotherapy arm.[2]

Microsatellite instability (MSI) status should not be used to contraindicate perioperative therapy. A recent Chinese meta-analysis of data from 501 patients in five clinical trials favored the use of adjuvant chemotherapy in MSI-High (MSI-H) patients, with an OS gain of 73% versus 60% (HR=0.62; 95% CI: 0.46-0.83; p=0.001) compared to observation.[3]

A recent study evaluated 295 patients with gastric cancer and esophagogastric junction cancer (≥ cT2 and/or N+) regarding the use of perioperative FLOT compared to the same regimen combined with atezolizumab (840 mg every 2 weeks, followed by atezolizumab 1,200 mg as monotherapy every 3 weeks for an additional 8 cycles).[4] Preliminary data show an increase in pCR with the use of atezolizumab (15% versus 24%) across all subgroups, with CPS being a predictive factor for pCR.[4] MSI-H

patients comprised 8% of the sample and achieved a pCR of 63% with the addition of immunotherapy.[4]

The randomized phase II PETRARCA study evaluated perioperative chemotherapy with FLOT in combination with trastuzumab and pertuzumab versus perioperative chemotherapy with FLOT in resectable HER-2-positive tumors.[5] This study found that perioperative anti-HER-2 therapy resulted in a higher pCR rate (35% versus 12%; p=0.02).[5] With a 22-month follow-up, median OS was not reached in either group.[5] The study suggests a PFS benefit for the group that received anti-HER-2 therapy (HR=0.58; p=0.14).[5]

Similar results were observed with the addition of durvalumab to FLOT in a randomized clinical trial.[6] The addition of durvalumab resulted in an increase in pCR (19% versus 7%), with no impact on surgical morbidity.[6]

The NEONIPIGA phase II study evaluated MSI-H patients exclusively. In this study, 32 patients with resectable gastric adenocarcinoma and esophagogastric junction cancer received a combination of ipilimumab and nivolumab as neoadjuvant therapy, followed by surgery and adjuvant nivolumab.[7] In a scenario where the benefit of neoadjuvant chemotherapy is questionable, the use of immunotherapy resulted in a pCR in 59% of cases, which is numerically higher than historical data for chemotherapy in this scenario (pCR around 10%).[7] During a 14.9-month follow-up, there was no disease recurrence, and only one patient died without evidence of disease.[7]

While perioperative chemotherapy has become the cornerstone of treatment, the role of perioperative chemoradiotherapy (CRT) remains an area of active investigation.[8] CRT, which combines chemotherapy with radiotherapy, aims to enhance local control by targeting microscopic residual disease and reducing the risk of locoregional recurrence. However, its routine use in the perioperative setting has produced mixed results.[8]

The CROSS trial, which investigated neoadjuvant CRT followed by surgery in esophageal and gastroesophageal junction cancers, demonstrated a significant survival benefit, leading to the adoption of this approach in specific subsets of patients.8 However, the applicability of these findings to gastric cancer remains uncertain, particularly given the anatomical and biological differences between these malignancies.[8]

Clinical trials, such as the TOPGEAR (Trial of Perioperative Chemotherapy versus Perioperative Chemoradiotherapy for Resectable Gastric Cancer), seek to clarify the role of CRT in gastric cancer.[9] Preliminary results suggest that CRT may offer additional benefits in patients with high-risk features, such as positive lymph nodes or poor response to chemotherapy.[9] However, the potential for increased toxicity, particularly gastrointestinal side effects, necessitates careful consideration.[9] The future of CRT in gastric cancer may lie in its integration with novel systemic therapies.[9] Combining CRT with targeted agents or immunotherapy could potentially enhance therapeutic efficacy while minimizing toxicity, but this approach remains largely experimental.[9] As more data emerge, the role of CRT in the perioperative management of gastric cancer will need to be re-evaluated, with a focus on patient selection and personalized treatment strategies.[9]

The indication for adjuvant nivolumab is based on the phase III CheckMate 577 study, in which 40% of the patients included had GEJ tumors. This study demonstrated a benefit in DFS (22.4 versus 11.2 months; HR=0.69; p=0.0003) and metastasis-free survival (28.3 versus 17.6 months; HR=0.74) with the application of nivolumab, 240 mg IV every 2 weeks for 4 months, followed by nivolumab, 480 mg IV monthly for 1 year in patients undergoing CRT followed by surgery, with absence of CRp.[14, 15]

Final considerations

The future of perioperative treatment for localized gastric cancer lies in the continued refinement of multimodal strategies.[10] Personalized treatment, guided by molecular profiling and biomarkers, will be essential to optimizing outcomes while minimizing toxicity.[11] The integration of novel therapies, including targeted agents and immunotherapy, holds great promise but requires further validation through well-designed clinical trials.[12] In addition to clinical advances, there is a need for global collaboration to address the disparities in gastric cancer outcomes across different regions.[12] The heterogeneity of gastric cancer, both in terms of molecular characteristics and epidemiology, necessitates a tailored approach that considers the unique challenges faced by different populations.[12]

In conclusion, the landscape of perioperative treatment for localized gastric cancer is rapidly evolving, with significant strides being made in improving survival and reducing recurrence.[13] As we continue to refine these approaches, the ultimate goal remains to provide patients with the most effective, personalized, and safe treatment options, paving the way for improved long-term outcomes and quality of life.[13]

References

1. Al-Batran SE, Hofheinz RD, Pauligk C, Kopp HG, Haag GM, Luley KB, Meiler J, Homann N, Lorenzen S, Schmalenberg H, Probst S, Koenigsmann M, Egger M, Prasnikar N, Caca K, Trojan J, Martens UM, Block A, Fischbach W, Mahlberg R, Clemens M, Illerhaus G, Zirlik K, Behringer DM, Schmiegel W, Pohl M, Heike M, Ronellenfitsch U, Schuler M, Bechstein WO, Königsrainer A, Gaiser T, Schirmacher P, Hozaeel W, Reichart A, Goetze TO, Sievert M, Jäger E, Mönig S, Tannapfel A. Histopathological regression after neoadjuvant docetaxel, oxaliplatin, fluorouracil, and leucovorin versus epirubicin, cisplatin, and fluorouracil or capecitabine in patients with resectable gastric or gastro-oesophageal junction adenocarcinoma (FLOT4-AIO): results from the phase 2 part of a multicentre, open-label, randomised phase 2/3 trial. Lancet Oncol. 2016 Dec;17(12):1697-1708. doi: 10.1016/S1470-2045(16)30531-9. Epub 2016 Oct 22. PMID: 27776843.

2. Cunningham D, Allum WH, Stenning SP, Thompson JN, Van de Velde CJ, Nicolson M, Scarffe JH, Lofts FJ, Falk SJ, Iveson TJ, Smith DB, Langley RE, Verma M, Weeden S, Chua YJ, MAGIC Trial Participants. Perioperative chemotherapy versus surgery alone for resectable gastroesophageal cancer. N Engl J Med. 2006 Jul 6;355(1):11-20. doi: 10.1056/NEJMoa055531. PMID: 16822992.

3. Nie RC, Chen GM, Yuan SQ, Kim JW, Zhou J, Nie M, Feng CY, Chen YB, Chen S, Zhou ZW, Wang Y, Li YF. Adjuvant Chemotherapy for Gastric Cancer Patients with Mismatch Repair Deficiency or Microsatellite Instability: Systematic Review and Meta-Analysis. Ann Surg Oncol. 2022 Apr;29(4):2324-2331. doi: 10.1245/s10434-021-11050-6. Epub 2021 Nov 18. Erratum in: Ann Surg Oncol. 2022 May;29(5):3193. doi: 10.1245/s10434-021-11151-2. PMID: 34796431.

4. Al-Batran SE, Lorenzen S, Thuss-Patience PC, Homann N, Schenk M, Lindig U, et al. Surgical and pathological outcome, and pathological regression, in patients receiving perioperative atezolizumab in combination with FLOT chemotherapy versus FLOT alone for resectable esophagogastric adenocarcinoma: Interim results from DANTE, a randomized, multicenter, phase IIb trial of the FLOT-AIO German Gastric Cancer Group and Swiss SAKK. Journal of Clinical Oncology. 2022 Jun 1;40(16_suppl):4003–3.

5. Hofheinz RD, Merx K, Haag GM, Springfeld C, Ettrich T, Borchert K, Kretzschmar A, Teschendorf C, Siegler G, Ebert MP, Goekkurt E, Mahlberg R, Homann N, Pink D, Bechstein W, Reichardt P, Flach H, Gaiser T, Battmann A, Oduncu FS, Loose M, Sookthai D, Pauligk C, Göetze TO, Al-Batran SE. FLOT Versus FLOT/Trastuzumab/Pertuzumab Perioperative Therapy of Human Epidermal Growth Factor Receptor 2-Positive Resectable Esophagogastric Adenocarcinoma: A Randomized Phase II Trial of the AIO EGA Study Group. J Clin Oncol. 2022 Nov 10;40(32):3750-3761. doi: 10.1200/JCO.22.00380. Epub 2022 Jun 16. PMID: 35709415.

6. Janjigian YY, Van Cutsem E, Muro K, et al. MATTERHORN: phase III study of durvalumab plus FLOT chemotherapy in resectable gastric/gastroesophageal junction cancer. Future Oncol. 2022.

7. Kelly RJ, Ajani JA, Kuzdzal J, Zander T, Van Cutsem E, Piessen G, et al. Adjuvant Nivolumab in Resected Esophageal or Gastroesophageal Junction Cancer. New England Journal of Medicine. 2021 Apr 1;384(13):1191–203.J Clin Oncol 39:abstr 4003, 2021.

8. Shapiro J, van Lanschot JJB, Hulshof MCCM, van Hagen P, van Berge Henegouwen MI, Wijnhoven BPL, van Laarhoven HWM, Nieuwenhuijzen GAP, Hospers GAP, Bonenkamp JJ, Cuesta MA, Blaisse RJB, Busch ORC, Ten Kate FJW, Creemers GM, Punt CJA, Plukker JTM, Verheul HMW, Bilgen EJS, van Dekken H, van der Sangen MJC, Rozema T, Biermann K, Beukema JC, Piet AHM, van Rij CM, Reinders JG, Tilanus HW, Steyerberg EW, van der Gaast A; CROSS study group. Neoadjuvant chemoradiotherapy plus surgery versus surgery alone for oesophageal or junctional cancer (CROSS): long-term results of a randomised controlled trial. Lancet Oncol. 2015 Sep;16(9):1090-1098. doi: 10.1016/S1470-2045(15)00040-6. Epub 2015 Aug 5. PMID: 26254683.

9. Leong T, Smithers BM, Haustermans K, Michael M, Gebski V, Miller D, Zalcberg J, Boussioutas A, Findlay M, O'Connell RL, Verghis J, Willis D, Kron T, Crain M, Murray WK, Lordick F, Swallow C, Darling G, Simes J, Wong R. TOPGEAR: A Randomized, Phase III Trial of Perioperative ECF Chemotherapy with or Without Preoperative Chemoradiation for Resectable Gastric Cancer: Interim Results from an International, Intergroup Trial of the AGITG, TROG, EORTC and CCTG. Ann Surg Oncol. 2017 Aug;24(8):2252-2258. doi: 10.1245/s10434-017-5830-6. Epub 2017 Mar 23. PMID: 28337660.

10. Sanchez-Vega F, Hechtman JF, Castel P, Ku GY, Tuvy Y, Won H, et al. EGFR mutation is associated with a poor outcome in locoregional, but not metastatic, gastric cancer. Ann Oncol. 2021;32(2):227-8.

11. Smyth EC, Nilsson M, Grabsch HI, van Grieken NC, Lordick F. Gastric cancer. Lancet. 2020;396(10251):635-48.

12. Lordick F, Mariette C, Haustermans K, Obermannová R, Arnold D. Oesophageal cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2016;27(suppl_5)

13. Van Cutsem E, Sagaert X, Topal B, Haustermans K, Prenen H. Gastric cancer. Lancet. 2016;388(10060):2654-64.

14. Kelly RJ, Ajani JA, Kuzdzal J, Zander T, Van Cutsem E, Piessen G, et al. Adjuvant Nivolumab in Resected Esophageal or Gastroesophageal Junction Cancer. New England Journal of Medicine. 2021 Apr 1;384(13):1191–203.

15. Ronan Joseph Kelly, Ajani JA, Kuzdzal J, Zander T, Eric Van Cutsem, Guillaume Piessen, et al. Adjuvant nivolumab (NIVO) in resected esophageal or gastroesophageal junction cancer (EC/GEJC) following neoadjuvant chemoradiotherapy (CRT): Expanded efficacy and safety analyses from CheckMate 577. Journal of Clinical Oncology. 2021 May 20;39(15_suppl):4003–3.

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