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REVIEW

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Efficacy of Anti-Epidermal Growth Factor Receptor Monoclonal Antibodies in Resectable Colon Cancer

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ABSTRACT The efficacy of anti-epidermal growth factor receptor (EGFR) monoclonal antibodies (MoAbs) has been proved in the treatment of left-sided RAS wild-type unresectable metastatic colorectal cancer. However, their effectiveness in the early stages of the disease has been questioned. Previous studies have shown that the use of these drugs in an adjuvant setting was not effective and recent evidence suggests that they are also ineffective in patients with resectable liver metastases. Neoadjuvant therapy is currently the standard of care for many types of cancer, and studies in this field are ongoing. There is limited data available on the efficacy of anti-EGFR MoAbs in the treatment of locally advanced colon cancer, and a recent study showed no benefit. This review focused on the perioperative use of anti-EGFR MoAbs in the treatment of resectable colon cancer and explored possible explanations for their low effectiveness.

Keywords: Colon cancer; cetuximab; panitumumab; anti-epidermal growth factor receptor; perioperative; neoadjuvant

Neoadjuvant therapy refers to a preoperative modality aimed at reducing the dimensions of a neoplasm before the surgical intervention or enhancing the probability of complete removal of the malignancy during surgery. It is also associated with several advantages, such as the eradication of micrometastases, reducing the possibility of distant recurrence, and the early assessment of tumor biology in response to treatment. However, it has potential drawbacks, including concerns about disease progression due to delayed surgery and the emergence of treatment-resistant clones.[1] Despite these drawbacks, neoadjuvant therapy has become the standard approach for several types of cancer, particularly rectal, esophageal, and gastric cancers. On the other hand, upfront surgery is the preferred treatment option for resectable non-metastatic colon cancer (CC). However, the results of a recently published FOxTROT trial have sparked debate about the potential utility of neoadjuvant therapy in CC.[2] According to the obtained results, the two-year risk of recurrence is reduced following a six-week neoadjuvant chemotherapy (ChT) in radiologically advanced (T3-4, N0-2, and M0) resectable locally advanced CC (LACC) as a result of computed tomography (CT) scanning. After the NICHE-2 trial, indicating the success of neoadjuvant immune checkpoint inhibitors in mismatch repair deficient (dMMR) LACC, the FOxTROT trial declared the effectiveness of neoadjuvant ChT in proficient mismatch repair (pMMR) LACC.[3]

The FOxTROT trial also indicated a crucial aspect of treatment, the effectiveness of anti-epidermal growth factor receptor (EGFR) monoclonal antibodies (MoAbs) in the neoadjuvant setting for resectable

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LACC. Several phase 3 studies have reported the effectiveness of anti-EGFR MoAbs [cetuximab (Cmab) and panitumumab (Pmab)] in the first-line treatment of left-sided RAS wild-type unresectable metastatic CC (mCC). However, somewhat surprising results have been reported in patients with resectable liver metastases. The phase 3 New EPOC trial declared the most robust data on the efficacy of Cmab in patients with resectable liver metastases of KRAS wild-type mCC.[4] In this trial, 259 patients were randomly assigned to the ChT with or without Cmab for 12 weeks, followed by surgery, followed by 12 weeks of ChT with or without Cmab groups. The study results were quite surprising. The median progression-free survival (PFS) in the ChT arm was 22.2 months compared to 15.5 months in the ChT plus Cmab arm [hazard ratio (HR): 1.17, 95% confidence interval (CI): 0.87-1.56]. The median overall survival (OS) was 81.0 months in the ChT arm and 55.4 months in the ChT plus Cmab arm (HR: 1.44, 95% CI: 1.02-2.05). In subgroup analysis, the results were similar in patients with BRAF wild-type or left-sided colon tumors. However, patients in the ChT plus Cmab arm showed progression at multiple sites and a higher number of premature deaths compared to the ChT arm. Therefore, the addition of Cmab to ChT appears to not only accelerate disease progression but also result in the development of more aggressive disease.

The effectiveness of anti-EGFR MoAbs, as a component of adjuvant therapy in CC, has been investigated in N0147 and PETACC-8 phase 3 trials. The N0147 trial initially used folinic acid, fluorouracil, and irinotecan (FOLFIRI) or folinic acid, fluorouracil, and oxaliplatin (FOLFOX) as the ChT backbone. However, after the recruitment of this trial, irinotecan showed no benefit in the adjuvant setting; thus, the FOLFIRI arm was closed, and the ChT continued using the FOLFOX regimen only.[5] In this trial, 1,863 patients with KRAS wild-type were randomly selected, with the primary endpoint being disease-free survival (DFS). Adding Cmab to FOLFOX did not improve three-year DFS and was numerically worse (74.6% vs. 71.5%, respectively; HR: 1.21, 95% CI: 0.98-1.49). A similar result was observed for the three-year OS (87.3% vs. 85.6%, respectively; HR: 1.25; 95% CI: 0.92-1.68). BRAF mutations were found in 18% of the study population. Even when these patients were excluded, the addition of Cmab did not increase efficacy (HR: 1.22, 95% CI: 0.96-1.56 for DFS; HR: 1.22, 95% CI: 0.82-1.81 for OS). Until discontinuation of the FOLFIRI regimen, 95 patients with RAS wild-type were included in this trial (69 patients in the FOLFIRI arm and 26 patients in the FOLFIRI plus Cmab arm). In additional analysis for these patients, there was a non-significant trendthere was a nonsignificant trend in favor of Cmab in DFS and OS (HR: 0.41, 95% CI: 0.14-1.17 for DFS; HR: 0.46, 95% CI: 0.13-1.56 for OS).[6] The PETACC-8 trial, with a similar design, randomized 1,602 patients with KRAS wild-type operated Stage III CC to either the FOLFOX or FOLFOX plus Cmab arms.[7] In this trial, there was no difference between the groups in terms of three-year DFS (75.1% vs. 78.0%, respectively; HR: 1.05, 95% CI: 0.85-1.29). In the subgroup analysis performed according to tumor localization, the addition of Cmab was found detrimental in right-sided tumors (HR: 1.40, 95% CI: 1.01-1.94). Although there was a trend in favor of Cmab in left-sided tumors, this difference was not significant (HR: 0.88, 95% CI: 0.67-1.15). In the analysis performed for RAS/RAF wild-type patients, 9% of patients with BRAF mutations were excluded from the analysis, and the addition of Cmab showed no benefit.

Even more limited data are available on the efficacy of anti-EGFR MoAbs in neoadjuvant therapy. The PRODIGE 22-ECKINOXE trial is a phase 2 study with a similar design to the FOxTROT trial.[8] In this trial, based on CT scan results, patients with clinically high-risk Stage 2-3 (T3, T4, and/or N2) CC, were randomized to six months of adjuvant FOLFOX (upfront surgery) or perioperative FOLFOX (neoadjuvant four cycles and eight cycles after) arms. In addition, a third arm was added that tested the addition of neoadjuvant Cmab to the perioperative arm in patients with KRAS wild-type. The primary endpoint was the tumor regression grade. After demonstrating a lack of efficacy in the Cmab arm in an interim analysis, this arm was stopped early. Until the discontinuation of this arm, 16 patients were included. The three-year DFS and OS were 68.75% and 87.50%, respectively, in the Cmab arm. The same survival out-

comes were 76.8% and 90.3%, respectively, in the ChT arm without perioperative Cmab. A small number of patients in the arm with Cmab were not powered for comparison with ChT, but were found to result in numerically lower survival rates. The FOxTROT study has produced the most substantial data to date regarding the neoadjuvant treatment utilizing anti-EGFR MoAbs, offering critical insights into the efficacy of this therapeutic approach. In this trial, patients with RAS wild-type CC in the perioperative arm were sub-randomized in a 1:1 ratio, depending on whether they could receive Pmab or not. A total of 279 patients participated in the FOLFOX with or without Pmab arms. The primary endpoint was residual disease or recurrence within two years. The addition of Pmab to FOLFOX did not result in any increase in efficacy in RAS wild-type CC patients. The tumor regression rate was 17% and 23% in the FOLFOX plus Pmab and FOLFOX arms, respectively [odds ratio (OR): 0.70, 95% CI: 0.38-1.27]. Although the two-year recurrence risk was numerically favoring the Pmab arm, there was no significant difference between the arms (13% vs. 18%, respectively; relative risk: 0.67, 95% CI: 0.36-1.23).

Evaluation of the current data and those obtained from the FOxTROT trial indicate that anti-EGFR MoAbs are ineffective in both LACC and mCC with resectable liver metastasis. How can we explain the failure of these drugs, which have proven their efficacy in the unresectable metastatic setting, to the resectable stage?. Although this issue remains unclear, several hypotheses have been suggested. The strongest pathophysiological hypothesis is that micrometastatic disease has different molecular characteristics than macrometastatic disease. The ability of epithelial-mesenchymal transformation is required for the migration of cancer cells from their primary sites to other sites. As the tumor grows, the E-cadherin responsible for cell-cell adhesion is suppressed, allowing cells to migrate through the epithelial-mesenchymal transition. When tumor cells reach their metastatic niche, E-cadherin suppression is abolished, and the reverse mesenchymal-epithelial transition begins. EGF/EGFR plays an important role in these processes.[9,10] Early use of anti-EGFR MoAbs may affect epithelial-mesenchymal transformation, and lead to the formation of resistant clones. Another hypothesis is the lack of biomarkers used in anti-EGFR MoAb selection. Currently, patients are selected according to RAS, RAF, and tumor localization in mCC. According to the mentioned studies, the addition of Cmab did not increase efficacy, even in BRAF wild-type and left-sided tumors. This gives the impression that the biomarkers used are insufficient in the early stages. Some biomarker studies have been carried out to elucidate this issue. According to the joint analysis results of the N0147 and PETACC-08 studies on MSI-H/dMMR status, the addition of Cmab to adjuvant FOLFOX was associated with shorter DFS in patients with sporadic dMMR. While the dMMR frequency is 4-5% in mCC, this rate increases to 15-20% in the early stages.[11] This suggests that tumors resistant to anti-EGFR in the early stage are 4-5 times more common than in the metastatic stage. Another biomarker is MicroRNA (miR)-31. The expression levels of miR-31-3p and miR-31-5p are associated with resistance to Cmab in CC.[12] The importance of this biomarker was evaluated in post hoc analyses of PETACC-08 and New EPOC studies.[13,14] Both studies showed that high miR-31 levels were associated with decreased response to Cmab. Apart from markers, such as dMMR and miR-31, many markers related to anti-EGFR resistance have been studied and were not detailed here, as they are associated with general resistance regardless of stage. However, even these two biomarkers suggest that treatment planning based on the RAS and RAF mutation status alone is insufficient in patient selection.

Another hypothesis is the effect of ChT agents combined with anti-EGFR MoAbs. It is accepted that there is no difference in efficacy in the combination of oxaliplatin or irinotecan with anti-EGFR MoAbs supported by several randomized studies. However, there is evidence, to the contrary, although not of the quality of randomized studies. This issue was examined in the joint analyses of the COIN (oxaliplatin-based with or without Cmab as first-line ChT) and PICOLLO (irinotecan-based with or without Pmab as second-line ChT) studies.[15,16] According to the joint analyses of these studies, after anti-EGFR plus irinotecan-based therapy, an increase in efficiency was observed in consensus molecular subtypes

(CMSs) 2-3 and 4.[17] However, following oxaliplatin-based treatment, the efficacy was limited in CMS 2 and 3. The adjuvant ChT trial NCCTG N0147 provides an opportunity to make inferences about the effect of ChT selection on efficacy. In this trial, there was a non-significant trend in survival in favor of the Cmab arm in an analysis of 146 patients included until the FOLFIRI arm was closed. However, the opposite result was observed when FOLFOX was used. This gives us the impression that anti-EGFR agents work more compatible with irinotecan. This may be of great importance in the failure of these agents, as most early-stage studies have used a combination of anti-EGFR MoAbs and FOLFOX. However, because irinotecan is ineffective in adjuvant therapy, a combination study to prove this hypothesis cannot be performed at an early stage. As a final hypothesis, there may be an inability to complete ChT due to the toxicity of anti-EGFR MoAbs. In the N0147 trial, the percentage of patients who completed 12 cycles of therapy was 79% in the FOLFOX arm compared to 67% in the FOLFOX plus Cmab arm. This rate became even more pronounced in patients aged 70 and over (80% vs. 57.5%, respectively). However, because the treatment intensity rates were similar between arms in PETACC-08, New EPOC, and FOxTROT studies, this hypothesis is limited to the N0147 trial only.

When the results of these trials and possible hypotheses are evaluated collectively, it can be concluded that according to our currently patient selection criteria, anti-EGFR MoAbs are not effective in resectable CC. However, further research is needed to address the discrepancy between the efficacy of these drugs in the unresectable metastatic setting and their ineffectiveness in the early stages of the disease. Until this issue is resolved, caution is advised in incorporating anti-EGFR MoAbs into neoadjuvant and adjuvant regimens for patients with resectable CC.

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Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

This study is entirely author's own work and no other author contribution.

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