Impact of Anti-EGFR Therapies on HER2-Positive Metastatic Colorectal Cancer (HER2+ mCRC): A Systematic Literature Review and Meta-Analyses of Clinical Outcomes

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Background

- Colon cancer (CRC) is a leading cause of cancer mortality accounting for 1.9 (1.8–2.0) million of new cancer cases and 0.84% of deaths (0.8–0.92) globally in 2021, with approximately 20.5% of patients diagnosed with CRC in Africa.
- Human epidermal growth factor receptor 2 (HER2) is overexpressed/amplified in 5–6% of patients with metastatic colorectal cancer (mCRC) and 3–5% of patients with resectable disease.
- HER2 overexpression/amplification in patients with mCRC (HER2+ mCRC) may be associated with resistance to standard of care anti-EGFR therapies.
- Meta-analyses have investigated the association between HER2 overexpression/amplification and resistance to anti-EGFR therapy in patients with mCRC.

Objective

- Our objective was to assess the predictive effect of HER2 amplification/overexpression on anti-EGFR treatment outcomes in mCRC patients.

Methods

- Systematic literature review of MEDLINE, EMBASE, and the Cochrane Library, covering 2001–2021, was conducted in June 2022 in accordance with the PRISMA guidelines.
- Studies evaluating progression-free survival (PFS), overall survival (OS), or overall response rate (ORR) in patients with mCRC-positive compared with HER2-negative (HER2-) mCRC who received anti-EGFR therapies and whose HER2 status was determined by immunohistochemistry, in-situ hybridization, or next-generation sequencing were included.
- Study quality was assessed using the Newcastle-Ottawa Scale, which grades studies in terms of population selection, comparability, and outcome assessment.

Meta-analysis

- Hazard ratios (HRs) that were directly reported in the included studies or calculated HRs (patient-level data that were extracted from Kaplan–Meier (KM) curves) were considered for the meta-analysis.
- Meta-analyses of proportions (OR) or HR (PFS, OS) were performed using random-effect models to account for the statistical heterogeneity.
- Pooled effect size measures were used for assessing the heterogeneity.

Results

- Hazard ratios were reported in the included studies or calculated HRs in the included studies.
- The included studies had a total of 167 publications.
- In the meta-analysis of 5 studies reporting PFS, there was a 2.84 times higher risk of death or progression (HR, 2.84 [95% CI, 1.73–4.66]) in HER2-positive (HER2+) patients compared with HER2-negative (HER2-) patients.
- In the meta-analysis of 18 studies reporting ORR, there was a 1.96 times higher risk of response to anti-EGFR treatment (OR, 1.96 [95% CI, 1.10–3.48]) in HER2-positive patients compared with HER2-negative patients.

Table 1. Characteristics of studies included in the meta-analysis

<table>
<thead>
<tr>
<th>Study</th>
<th>Study population</th>
<th>Sample size</th>
<th>Median age (years)</th>
<th>Male sex (%)</th>
<th>HER2 status</th>
<th>Treatment</th>
<th>Progression-free survival</th>
<th>Overall survival</th>
<th>Overall response rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>2020</td>
<td>159/262 (159/159)</td>
<td>201/227 (201/201)</td>
<td>64/64 (64/64)</td>
<td>70/70 (70/70)</td>
<td>159/262 (159/159)</td>
<td>Therapy</td>
<td>0.125</td>
<td>0.125</td>
<td></td>
</tr>
<tr>
<td>2021</td>
<td>20/26 (20/26)</td>
<td>18/33 (18/18)</td>
<td>60/60 (60/60)</td>
<td>70/70 (70/70)</td>
<td>20/26 (20/26)</td>
<td>Therapy</td>
<td>0.125</td>
<td>0.125</td>
<td></td>
</tr>
<tr>
<td>2016</td>
<td>36/50 (36/36)</td>
<td>46/67 (46/46)</td>
<td>60/60 (60/60)</td>
<td>70/70 (70/70)</td>
<td>36/50 (36/36)</td>
<td>Therapy</td>
<td>0.125</td>
<td>0.125</td>
<td></td>
</tr>
<tr>
<td>2019</td>
<td>50/67 (50/50)</td>
<td>67/100 (67/67)</td>
<td>60/60 (60/60)</td>
<td>70/70 (70/70)</td>
<td>50/67 (50/50)</td>
<td>Therapy</td>
<td>0.125</td>
<td>0.125</td>
<td></td>
</tr>
</tbody>
</table>

Limitations

- The studies included in this meta-analysis were of a retrospective design, and may be limited by selection and publication bias.
- Meta-analysis exclusion assessed a total of 144 studies excluding the included studies.
- Regimens used in the included studies often comprised combination treatments with standard chemotherapy, which may not be representative of current clinical practice.
- Survival analysis was limited by insufficient follow-up data reported in the literature, and subsequent registries reviewed were not received.

Conclusions

- In patients with HER2+ mCRC treated with anti-EGFR therapy, HER2 overexpression/amplification is associated with worse PFS and OS.
- HER2 testing should be considered to help optimize treatment choices for patients with mCRC in routine practice.

References

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