Anti-epidermal or anti-vascular endothelial growth factor as first-line metastatic colorectal cancer in modified Glasgow prognostic score 2’ patients

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Abstract

Background In metastatic colorectal cancer, the modified Glasgow prognostic score (mGPS) has been approved as an independent prognostic indicator of survival. No data existed on poor prognosis patients treated with molecular-targeted agents.

Methods From January 2007 to February 2012, patients with metastatic colorectal cancer and poor predictive survival score (mGPS = 2), treated with 5-fluorouracil-based chemotherapy in addition to an anti-epidermal growth factor receptor (EGFR) or anti-vascular epidermal growth factor (VEGF) therapy, were included to assess the interest of targeted therapy within mGPS = 2’ patients.

Results A total of 27 mGPS = 2’ patients were included and received a 5-fluorouracil-based systemic chemotherapy in addition to an anti-EGFR treatment (cetuximab; n = 18) or an anti-VEGF treatment (bevacizumab; n = 9). Median follow-up was 12.1 months (interquartile range 4.9–22). Patients were Eastern Cooperative Oncology Group (ECOG) Performance Status 1, 2, and 3 in 66% (n = 18), 26% (n = 7), and 8% (n = 2), respectively. Comparing anti-EGFR and anti-VEGF groups, median progression-free survival was 3.9 and 15.4 months, respectively, and was significantly different (P = 0.046). Conversely, the median overall survival was not significantly different between the two groups (P = 0.15).

Conclusion Our study confirmed the poor survival of patients with mGPS = 2 despite the use of targeted therapy and identified the superiority of an anti-VEGF treatment in progression-free survival, without a significant benefit in the overall survival compared with the anti-EGFR therapy. Our results deserved confirmation by a prospective clinical trial.

Keywords Colorectal cancer; C-reactive protein; Glasgow prognostic score; Targeted therapy; Bevacizumab; Cetuximab; Vascular epithelial growth factor; Epidermal growth factor receptor

Introduction

Colorectal cancer is the most common digestive cancer worldwide and the third leading cause of cancer death in western countries. The development of targeted therapies in metastatic colorectal cancer (mCRC) helped to improve the overall survival from a few months to more than 32 months. Two targeted therapies, the epidermal growth factor receptor (EGFR)-targeting and the vascular epidermal growth factor (VEGF)-targeting monoclonal antibodies, have improved overall survival when added to standard chemotherapy in first-line mCRC, compared with chemotherapy alone. There is increasing evidence that the presence of a systemic inflammatory response defined by an elevated C-reactive protein level and hypoalbuminemia is a prognostic indicator in patients with various types of cancer. Of note, elevated C-reactive protein levels and low albumin concentrations are associated with poor overall survival in case of tumoural digestive disease. Initially, the Glasgow prognostic score (GPS) was constructed with a C-reactive protein limit of 10 mg/L. A down modification of the C-reactive protein limit to 5 mg/L has permitted better accuracy to detect patients with a poor clinical outcome and defined the modified GPS (mGPS). Indeed, the mGPS has been reported as one of the
most useful prognostic indicators of survival in mCRC' patients. An mGPS score of 2 was associated with poorer overall survival in patients receiving a targeted therapy in addition to chemotherapy. The aim of this retrospective study was to evaluate the benefit of the anti-EGFR or the anti-VEGF therapy in addition to the chemotherapy in mGPS = 2 patients.

Materials and methods

Study design

From January 2007 to February 2012, consecutive mCRC patients with a poor predictive indicator of survival (mGPS = 2) and who received 5-fluorouracil-based chemotherapy with an anti-EGFR therapy (cetuximab) or an anti-VEGF therapy (bevacizumab), as first-line treatment, were included in the present analysis. Patients were eligible in this retrospective study if they met the following criteria: advanced pathologically proven mCRC, age > 18 years, adequate renal function (creatinine clearance > 40 mL/min), Eastern Cooperative Oncology Group (ECOG) Performance Status (PS), C-reactive protein > 5 mg/L, and albumin concentration < 3.5 g/dL before treatment initiation. Patients receiving anti-EGFR treatment had no KRAS mutations of exon 2 codons 12 and 13. Blood samples were obtained for the measurement of white blood cell (WBC) count, albumin, and C-reactive protein concentrations by laboratory. The coefficient of variation for these methods, over the range of measurement, was less than 5% as established by routine quality control procedures. The mGPS, a biological score, was described in previous publication. Briefly, patients with both an elevated C-reactive protein (>5 mg/L) and hypoalbuminemia (<3.5 g/dL) were allocated a score of 2. Patients in whom only one of these biochemical abnormalities was present were allocated a score of 1. If no abnormality was present, patients were allocated a score of 0. Tumour evaluation (using computerized tomography scan) was performed every six cycles of treatment, or earlier if clinically indicated, according to RECIST v1.0. Progression-free survival and overall survival were measured from the date of first treatment administration to the date of disease progression or death for the former and the date of death for the latter (Figures 1 and 2). Patients received 5-fluorouracil-based chemotherapy in addition to cetuximab or bevacizumab after digestive oncology multidisciplinary staff approval and in line with the French recommendations for treatment of mCRC. This study has received ethics approval from our local Human Research Ethics Committee.

Statistics

All data were reviewed and controlled by the principal investigator. Qualitative data were expressed as numbers and percentages. The quantitative descriptive analysis was presented as median (interquartile range). Univariate survival analysis was performed using the Kaplan–Meier method with the log-rank test. Deaths up to 1 January 2014 were included in the analysis. A probability (P) value of 0.05 was considered significant. Statistical analysis was performed using GraphPad Prism 6.0 software (GraphPad Software Inc., San Diego, CA, USA).

Results

A total of 27 mGPS = 2’ patients were included and received a 5-fluorouracil-based chemotherapy in addition to an anti-EGFR treatment (n = 18) or an anti-VEGF treatment (n = 9). Systemic cytotoxic chemotherapy was 5-fluorouracil plus either oxaliplatin (FOLFOX regimen) or irinotecan (FOLFIRI regimen) in 20 and 7 patients, respectively. Clinical characteristics between the two groups are shown in Table 1. Median follow-up was 12.1 months (interquartile range 4.9–22).
Patients were ECOG PSs 1, 2, and 3 in 66% (n = 18), 26% (n = 7), and 8% (n = 2), respectively. Median progression-free survival was 3.9 months in patients receiving the anti-EGFR treatment vs. 15.4 months in the anti-VEGF group [Hazard Ratio (HR) = 0.42; confidence interval (CI) 95% (0.18–0.98), P = 0.046]. Median overall survival was 11.6 months in patients receiving the anti-EGFR treatment vs. 20.1 months in the anti-VEGF group [HR = 0.48; CI 95% (0.18–1.29), P = 0.15]. In the anti-VEGF group, 33% of patients (n = 3) had a KRAS mutation of exon 2 codons 12 or 13. Patients with an ECOG PS ≤ 1 had a median overall survival of 14.5 months vs. 6.0 months in patients with an ECOG PS ≥ 2. In mGPS = 2’ patients, the ECOG PS was not a significant predictor of survival [HR = 0.44; CI 95% (0.14–1.42), P = 0.17].

**Discussion**

In the present study, we confirmed the poor survival of patients with mGPS = 2, despite the use of targeted therapy, with 11.6 and 20.1 months in both groups. The observed median overall survival was more than 12 months shorter than those recently published in patients receiving first-line treatment with a targeted therapy: 23.9–34.2 and 25–30 months using an anti-EGFR and an anti-VEGF, respectively. This discrepancy reinforced the usefulness of an mGPS evaluation at baseline.

Better discrimination is needed to improve therapeutic decisions. A combination model of prognostic and predictive factors could lead to a better selection of patients before initiating treatment. In the literature, prognostic classifications were proposed to predict the clinical outcome in treated mCRC patients. In patients receiving 5-fluorouracil-based chemotherapy, Köhne et al. identified clinical and biological prognostic markers associated with a worse survival. The stratification on PS (ECOG PS), alkaline phosphatase level, the number of metastatic sites, and WBC count permitted to classify patients in good, intermediate, and poor Köhne’s prognostic groups. This categorization of mCRC patients has defined a valid prediction of the clinical risk (Köhne model). At the era of targeted therapy, relevance of Köhne’s risk classification was questioned in a recent study. Desot et al. observed a significant survival difference between good and poor prognostic groups (P < 0.01) and between intermediate and poor prognostic groups (P < 0.01) but not between good and intermediate prognostic groups (P = 0.5). A complementary approach using two baseline parameters (World Health Organization PS and serum Lactate dehydrogenase (LDH) level) was proposed and proved its efficacy in patient stratification. In our study, we confirmed the worsening

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**Table 1 Clinical characteristics at baseline and univariate survival analysis in modified Glasgow prognostic score = 2’ patients with metastatic colorectal cancer receiving 5-fluorouracil-based chemotherapy in addition to anti-epidermal growth factor receptor (EGFR) or anti-vascular epidermal growth factor (VEGF) (n = 27)**

<table>
<thead>
<tr>
<th>Variable</th>
<th>All patients (n = 27) n (%)</th>
<th>Overall survival* (months)</th>
<th>Anti-EGFR group (n = 18) n (%)</th>
<th>Anti-VEGF group (n = 9) n (%)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Performance status (ECOG)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤1</td>
<td>18 (66)</td>
<td>14.5 (5.3–24.2)</td>
<td>10 (55)</td>
<td>8 (89)</td>
<td>NS</td>
</tr>
<tr>
<td>≥2</td>
<td>9 (32)</td>
<td>6.0 (3.6–13.7)</td>
<td>8 (45)</td>
<td>1 (11)</td>
<td></td>
</tr>
<tr>
<td>Primary tumour site</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right colon</td>
<td>6 (22)</td>
<td>4.5 (2.8–10.5)</td>
<td>3 (16)</td>
<td>3 (33)</td>
<td>NS</td>
</tr>
<tr>
<td>Transverse colon</td>
<td>4 (15)</td>
<td>7.7 (5.8–20.5)</td>
<td>3 (16)</td>
<td>1 (11)</td>
<td></td>
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<tr>
<td>Left colon</td>
<td>12 (44)</td>
<td>15 (5.5–21.7)</td>
<td>8 (44)</td>
<td>4 (44)</td>
<td></td>
</tr>
<tr>
<td>Rectum</td>
<td>5 (19)</td>
<td>8.2 (4.5–12.5)</td>
<td>4 (24)</td>
<td>1 (12)</td>
<td></td>
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<tr>
<td>Number of metastatic sites</td>
<td></td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>≥1</td>
<td>15 (55)</td>
<td>11.1 (6.3–21.2)</td>
<td>11 (61)</td>
<td>4 (44)</td>
<td>NS</td>
</tr>
<tr>
<td>≥2</td>
<td>11 (40)</td>
<td>18.3 (8.8–23)</td>
<td>6 (33)</td>
<td>5 (56)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>1 (5)</td>
<td>17.8</td>
<td>1 (6)</td>
<td>0</td>
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<tr>
<td>KRAS exon 2 status</td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Wild type</td>
<td>24 (88)</td>
<td>6.3 (4–11.9)</td>
<td>18 (100)</td>
<td>6 (67)</td>
<td>NS</td>
</tr>
<tr>
<td>Mutated</td>
<td>3 (12)</td>
<td>24 (13.6–31)</td>
<td>0</td>
<td>3 (33)</td>
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<tr>
<td>BRAF mutation</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td></td>
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<tr>
<td>Lymphocytes</td>
<td></td>
<td></td>
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<tr>
<td>&lt;1000/mm³</td>
<td>4 (15)</td>
<td>6.4 (5.6–22)</td>
<td>3 (17)</td>
<td>1 (11)</td>
<td>NS</td>
</tr>
<tr>
<td>&gt;1000/mm³</td>
<td>23 (85)</td>
<td>6.5 (3.5–20.9)</td>
<td>15 (83)</td>
<td>8 (89)</td>
<td></td>
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<tr>
<td>Haemoglobin</td>
<td></td>
<td></td>
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<tr>
<td>&lt;10 × 10³/L</td>
<td>10 (37)</td>
<td>6.2 (3.9–16.7)</td>
<td>8 (44)</td>
<td>2 (22)</td>
<td>NS</td>
</tr>
<tr>
<td>≥10 × 10³/L</td>
<td>17 (63)</td>
<td>6.4 (3.3–24)</td>
<td>10 (56)</td>
<td>7 (78)</td>
<td></td>
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<tr>
<td>C-reactive protein (mg/L)</td>
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<td></td>
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<td></td>
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<tr>
<td>&lt;20 × 10³/L</td>
<td>33 (20–62)</td>
<td>33 (19–65)</td>
<td>33 (20.7–47)</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>&gt;20 × 10³/L</td>
<td>32 (29–33)</td>
<td>32 (29.5–33)</td>
<td>32 (28–33)</td>
<td>NS</td>
<td></td>
</tr>
</tbody>
</table>

ECOG, Eastern Cooperative Oncology Group; NS, Not Significant.
P < 0.05 is considered significant.
*Median (interquartile range).
A study compared patients with a poor clinical status (ECOG PS of 3 or 4) who did not respond to cetuximab or who had lung mCRC, with a survival benefit in this mCRC population. 

Inoue et al. identified the usefulness of its biological score as an independent prognostic indicator of survival in patients undergoing multimodality therapy for mCRC, especially prior chemotherapy [odds ratio 1.858; 95% CI 1.213–2.846, \( P = 0.0044 \)]. In their prospective randomized controlled study, all patients were treated with 5-fluorouracil-based chemotherapy. 

Among the patients who received cetuximab, the Kaplan-Meier survival curves were significantly different between mGPS 0, 1, and 2: 38.2, 14, and 12.1 months, respectively (\( P = 0.0093 \)). Interestingly, the mGPS score was not able to identify patients with prolonged progression-free survival when patients received an anti-VEGF treatment. In the present study focusing on mGPS = 2 patients, those receiving an anti-VEGF treatment had a shorter progression-free survival than those using an anti-VEGF, but the benefit was not observed in the overall survival.

Maillet et al. confirmed the interest of the mGPS to predict response to an anti-VEGF targeted therapy in addition to conventional chemotherapy. In their study, the median overall survival was 20.1, 11.4, and 6.5 months in the GPS 0, 1, and 2 groups, respectively (\( P = 0.03 \)). In mGPS = 2 patients, anti-VEGF toxicity could be more frequent and severe, especially in case of deep denutrition. It has been identified that bevacizumab-induced hypertension is a common toxicity, which could be a marker of treatment efficacy. Meanwhile, long exposure to anti-angiogenic agents may expose to rare side effects as posterior reversible encephalopathy syndrome or pneumonitis intestinalis. In our study, we identified a benefit in patients receiving the anti-VEGF therapy as compared to anti-EGFR (\( P = 0.046 \)). Our results reinforced the importance of the utilization of the mGPS in patients with mCRC. Given the poor overall survival seen in patients with an mGPS = 2, we postulate that the use of the mGPS could help better identifying mCRC patients who could derive benefit from intensive treatments. So, we identified the superiority of an anti-VEGF treatment in progression-free survival, without a significant benefit in the overall survival compared with the anti-EGFR therapy.

To conclude, our data reinforced the importance of a clinical and a biological evaluation, using the mGPS score in patients receiving targeted agents for mCRC. ECOG PS appeared not efficient enough for the evaluation at baseline to identify long survivors. Our study deserved clinical trials based on mGPS score.

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Conflict of interest
None declared.

References


