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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

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Introduction

Colorectal cancer is the most common digestive cancer worldwide and the third leading cause of cancer death in western countries.[1] 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.[2] 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.[3,4]

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.[5,6] Of note, elevated C-reactive protein levels and low albumin concentrations are associated with poor overall survival in case of tumoural digestive disease.[7] 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).[8] Indeed, the mGPS has been reported as one of the

most useful prognostic indicators of survival in mCRC' patients.[9] An mGPS score of 2 was associated with poorer overall survival in patients receiving a targeted therapy in addition to chemotherapy.[10] 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

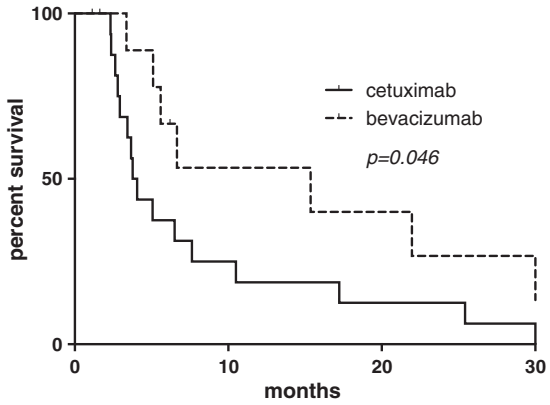
Study design

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.[11] Briefly, patients with both an elevated C-reactive protein ($>$5 mg/L) and hypoalbuminemia ($<$35 g/L) 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).

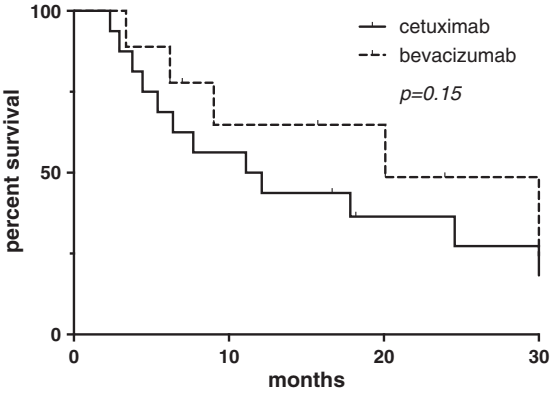
Figure 1 Progression-free survival in anti-epidermal growth factor receptor and anti-vascular epidermal growth factor groups.



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).

Figure 2 Overall survival in anti-epidermal growth factor receptor and anti-vascular epidermal growth factor groups.



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[12,13] and an anti-VEGF,[14,15] 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).[16] At the era of targeted therapy, relevance of Köhne's risk classification was questioned in a recent study.[17] 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.[18] In our study, we confirmed the worsening

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) ($n = 27$)

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

ECOG, Eastern Cooperative Oncology Group; NS, Not Significant.
$P < 0.05$ is considered significant.
*Median (interquartile range).

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prognosis of patients with an mGPS = 2 despite the use of targeted therapy in metastatic colorectal carcinoma. The implication of biological or clinical prognosis score such as mGPS, ECOG PS, WBC, and LDH should be developed for a better identification of patients with a poor prognosis.

The mGPS has proved its efficiency as a prognostic marker in mCRC,[9] to assess the tolerance of systemic chemotherapy,[5] and was a predictor of cancer-related death after surgery.[19] It could also help identify unfit mCRC patients, in whom first-line chemotherapy regimens should be adapted to comorbidities and poor ECOG PS.[20] 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, $P = 0.0044$].[21] In their retrospective study, all patients were treated with 5-fluorouracil-based-cytotoxic chemotherapy, and 21% received a targeted treatment. In line with Inoue, we previously outlined in mCRC the usefulness of the mGPS score to identify patients with poor overall survival despite the utilization of anti-VEGF or anti-EGFR agents.[22,10] Patients with a poor ECOG PS (>1) derive similar benefit from superior treatment as patients with PS of 0–1 but with an increased risk of toxicities.[23] It has been previously published that 90% of mGPS = 2' patients were ECOG PS = 1 suggesting a lack of efficacy of the ECOG PS indicator to identify patients who didn't take advantage of treatment.[20] In line with those results, our single-centre study confirmed a poor overall survival in patients with mGPS = 2 and suggested a benefit in such situation for the use of anti-VEGF therapy. However, due to the small number of patients, those data deserved to be confirmed in a prospective randomized study.

Molecular-targeted agents' anti-VEGF and anti-EGFR received a Federal Drugs Approval and the European Medicines Agency approval in first-line mCRC. Lievre *et al*. confirmed the high prognostic value of KRAS mutations on response to cetuximab and survival in mCRC patients.[24] More recently, Douillard *et al*. pinpointed a deleterious effect in patients receiving anti-EGFR treatment with no KRAS mutations in exon 2 but with other mutations on KRAS or NRAS.[25] Considering the utilization of the anti-EGFR therapy, the approval was restricted in 2013 to KRAS (exons 2, 3, and 4) and NRAS (exons 2, 3, and 4) wild-type mCRC. In the prime study, Douillard *et al*. identified a 16% mutations rate not located on KRAS exon 2.[13] In our study, KRAS exon 2 analysis was performed without other KRAS or NRAS search for mutations. Therefore, one hypothesis of the identified lack of efficacy in mGPS = 2' patients receiving an anti-EGFR treatment might be due to the presence of other mutations on KRAS or NRAS.

Inoue *et al*. and others reported the value of the mGPS using 5-fluorouracil-based chemotherapy in addition to an anti-EGFR therapy in first-line treatment of mCRC.[21,22] Patients with poor ECOG PS (3 or 4) seemed not to benefit from the addition of a molecular-targeted agent.[26] The anti-EGFR therapy used in addition to cytotoxic chemotherapy was suggested with an acceptable toxicity profile in selected patients.[3] The toxicity profile of targeted therapies restricted their utilization to patients in better conditions than those included in the present study. Biological inflammation induced asthenia. Asthenia is a complex symptom dominated by fatigue of a pathological degree.[27] In our study, patients with an important inflammatory response had a non-significantly higher rate of ECOG PS, which might be considered as targeted therapy toxicity and induced a dose reduction. This heightens the importance of evaluating therapeutic drugs by a clinical and biological prognostic indicator. Kishi *et al*. previously published a prognostic biological score: the blood neutrophil-to-lymphocyte ratio. A neutrophil-to-lymphocyte ratio > 5 was associated with a worse survival in liver mCRC' patients treated with systemic chemotherapy.[28] The mGPS score in the era of anti-EGFR therapy in first-line treatment of mCRC' patients has been evaluated and validated as a significant predictor of overall survival with a median overall survival in the mGPS 0, 1, and 2 of 38.2, 14, and 12.1 months, respectively ($P = 0.0093$).[22] Interestingly, the mGPS score was not able to identify patients with prolonged progression-free survival when receiving an anti-EGFR treatment. In the present study focusing on mGPS = 2 patients, those receiving an anti-EGFR treatment had a shorten progression-free survival than those using an anti-VEGF, but the benefit was not observed in considering 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 ($P = 0.03$).[10] In mGPS = 2' patients, anti-VEGF' toxicities could be more frequent and severe, especially in case of deep denutrition.[29] It has been identified that bevacizumab-induced hypertension is a common toxicity, which could be a marker of treatment efficacy.[30] Meanwhile, long exposure to anti-angiogenic agents may expose to rare side effects as posterior reversible encephalopathy syndrome[31] or pneumatosis intestinalis.[32] In our study, we identified a benefit in patients receiving the anti-VEGF therapy vs. 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 an mCRC. ECOG PS appeared not efficient enough for the evaluation at baseline to identified long survivors. Our study deserved clinical trials based on mGPS score.

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Conflict of interest

None declared.

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