

Predictive factors for the efficacy of cetuximab plus chemotherapy as salvage therapy in metastatic gastric cancer patients

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Abstract

Purpose We performed a retrospective study to evaluate the efficacy of cetuximab plus chemotherapy in metastatic gastric cancer (MGC) patients previously treated with chemotherapy and to investigate potential predictors of treatment efficacy in those patients.

Methods Thirty-two patients with MGC were included in this study. Cetuximab was delivered, often combined with irinotecan-based chemotherapy. Thirty patients were analyzed for K-ras mutations via direct sequencing of the tumor DNA.

Results Patients were heavily pretreated with a median number of three previous lines of palliative chemotherapy (56% of the patients were refractory to all of the following drugs: fluoropyrimidines, cisplatin, irinotecan, oxaliplatin, and docetaxel) and 53% of the patients displayed poor performance status. Of 28 response-assessable patients, the overall response rate to cetuximab plus chemotherapy was 3.6% [95% confidence interval (CI) 0–10.5%] and the disease control rate was 28.6%. The median progression-free survival (PFS) was 1.7 months (95% CI 1.3–2.1 months), and the median overall survival (OS) was 3.2 months (95% CI 1.4–5.0 months). Multivariate analyses revealed that skin rash and performance status were significantly associated with PFS and OS. The presence of a K-ras mutation (13.3%) was not associated with either PFS or OS.

Conclusion Our study suggests that MGC patients with good performance status and skin rash benefit most from salvage cetuximab combined with chemotherapy, even in heavily pretreated status.

Keywords Gastric cancer · Cetuximab · Chemotherapy · Skin rash · Performance status · K-ras · Predictor

Introduction

Despite its decreasing incidence over the past few decades, gastric cancer remains a global health issue; it is the second most common cause of cancer deaths worldwide [1]. Although a survival benefit has been demonstrated by systemic chemotherapy in patients with locally advanced or metastatic gastric cancer (MGC) [2, 3], the benefits of combination chemotherapy have been modest, even with modern agents such as oral fluoropyrimidines, irinotecan, oxaliplatin, and taxanes [4–9]. Therefore, more effective treatments are needed to improve survival in these patients.

Recently, an increased understanding of the molecular basis of cancer has led to the development of specific molecule-targeted agents. One example is the epidermal growth factor receptor (EGFR), a member of the tyrosine kinase growth factor receptor superfamily that is overexpressed in a variety of cancers, including gastric cancer (10.4–63%) [10–14]. In addition, EGFR overexpression is associated with tumor progression and poor prognosis in gastric cancer [11, 12, 14]. EGFR expression was, however, a positive prognostic factor for overall survival (OS) in gastric cancer patients who underwent curative resection followed by adjuvant chemotherapy with 5-fluorouracil and cisplatin; relative risk of death 0.475 [95% confidence interval (CI) 0.282–0.791], $P = 0.005$ [15]. The variations of the results

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between different studies might be due to heterogeneity of EGFR expression within the tumor and different methodological setups. Several techniques can be used for measuring EGFR expression, including immunohistochemistry (IHC), reverse transcriptase polymerase chain reaction (PCR), and fluorescence in situ hybridization (FISH). Although IHC is the most widely used method for determining EGFR expression, its value is limited by lack of methodological standardization. In addition, there has been a controversial relationship between EGFR protein expression as detected by IHC and gene copy number detected by FISH [15, 16]. The prognostic role of EGFR expression and the best approach to measuring EGFR in gastric cancer need to be further validated.

Agents targeting EGFR, such as cetuximab, are in clinical use. Cetuximab, a chimeric IgG1 monoclonal antibody (mAb) directed at the EGFR binding site, has demonstrated activity in a variety of cancers, including colorectal cancer and head and neck cancer, in both first-line and refractory settings [17, 18]. Interestingly, skin toxicity that evolves during the first weeks of cetuximab treatment has been identified as a potent predictor of the response to it [19, 20]. The K-ras mutation has recently been demonstrated as a predictive factor for resistance to cetuximab [21–24].

In gastric cancer, several phase II trials of cetuximab plus chemotherapy have shown promising results, mainly in chemo-naïve patients with advanced gastric or gastroesophageal junction adenocarcinoma [25–32]. However, limited data on the efficacy and predictors for success of cetuximab salvage therapy are available for heavily pretreated patients with gastric cancer.

The aim of this study was (1) to evaluate the efficacy of cetuximab-containing therapy in MGC patients previously treated with one or more chemotherapy regimens and (2) to investigate predictors of treatment efficacy in those patients.

Patients and methods

Patients and treatment

We retrospectively reviewed 32 consecutive MGC patients who had received cetuximab plus chemotherapy as salvage therapy after failure of one or more systemic cytotoxic chemotherapies between July 2006 and June 2008 at the Research Institute and Hospital, National Cancer Center, Korea. All of these patients had a histologically proven gastric adenocarcinoma.

Cetuximab was delivered at an initial dose of 400 mg/m² i.v., followed by weekly doses of 250 mg/m², most often along with a combination of irinotecan-based chemotherapy: weekly irinotecan (*n* = 24), biweekly irinotecan/

infusional 5-fluorouracil (5-FU)/leucovorin (LV) (*n* = 2), biweekly irinotecan/cisplatin (*n* = 1), biweekly oxaliplatin/5-FU/LV (*n* = 3), or docetaxel ± cisplatin (*n* = 2). Treatment was continued until disease progression, unacceptable toxicity, or patient's refusal.

Chemotherapy was delayed until absolute neutrophil counts were $\geq 1.5 \times 10^9 \text{ L}^{-1}$ (or $1.0 \times 10^9 \text{ L}^{-1}$ if leukocyte counts were $\geq 3.0 \times 10^9 \text{ L}^{-1}$), platelet counts were $\geq 75 \times 10^9 \text{ L}^{-1}$, and other non-hematological toxicity was \leq grade 1. Chemotherapy doses were reduced by 20% for grade 4 myelosuppression, grade 3/4 febrile neutropenia or non-hematological toxicity, or recurrent grade 2 diarrhea or abdominal pain. Administration of granulocyte-colony stimulating factor was permitted in patients with grade 4 neutropenia or grade 3/4 febrile neutropenia.

An institutional review board at the Research Institute and Hospital, National Cancer Center, Korea, reviewed and approved this study. Patient consent for analysis of stored biological samples and relevant clinical data were verified for all patients included.

Evaluation of treatment efficacy

Tumor response was evaluated by computed tomography (CT) scan according to the Response Evaluation Criteria in Solid Tumors (RECIST) [33]. CT scans were performed within 4 weeks of treatment initiation and were repeated every 6–8 weeks during treatment. Responses were confirmed by subsequent CT scans at least 4 weeks after documentation of the initial response. Skin toxicity was graded according to the National Cancer Institute Common Toxicity Criteria, version 3.0. These criteria indicated that an acne-like skin rash not requiring intervention was grade 1, that requiring intervention was grade 2, and that being associated with pain, disfigurement, ulceration, or desquamation was grade 3.

DNA extraction and K-ras mutation analyses

K-ras mutation analyses were performed in 30 patients and the remaining 2 patients were excluded because tumor samples were unavailable. Tumor samples were obtained from the primary gastric tumor (*n* = 25), metastatic tissue (*n* = 2), or both (*n* = 3).

DNA was extracted from formalin-fixed paraffin-embedded (FFPE) tissue sections with the QIAmp DNA Mini Kit (Qiagen, Hilden, Germany) according to the manufacturer's protocol. For FFPE tissues, samples were obtained after histologic verification of the presence of tumor cells (>70%) in each tumor sample.

The presence of K-ras point mutations was assessed in codons 12 and 13, two hotspots that include more than 95% of the mutations in this gene [34]. The primers used for

K-ras gene analysis were 5'-ACTGAATATAAACTTGTGGTAGTTGGACCT-3' (forward) and 5'-TCAAAGAATGGTCTGGACC-3' (reverse). The PCR reaction mixture (20 μ l) contained approximately 0.1 μ g of genomic DNA in 20 mM Tris hydrochloride (pH 8.4), 50 mM potassium chloride, 2.0 mM magnesium chloride, 0.2 mM each of deoxyribonucleoside triphosphate, 0.2 μ M of each primer, and 5 U of f-Taq DNA polymerase (Solgent, Daejeon, Korea). Templates were initially denatured for 5 min at 94°C, followed by 35 cycles of PCR with incubations of 1 min at 94°C, 1 min at 55°C, and 1 min at 72°C. The reaction was incubated at 72°C for 5 min during the last cycle. PCR reactions were checked for appropriate amplification by running the DNA fragments in an ethidium bromide-stained agarose gel and visualizing the bands by UV light transillumination.

PCR products were purified with a QIAquick PCR purification kit (Qiagen, Valencia, USA) and then sequenced with an ABI3130x1 DNA sequencer (Applied Biosystems, Foster City, USA) using dye-primer conditions recommended by the manufacturer. In each case, the detected mutation was confirmed in the sequence of both the sense and antisense strands.

Statistical methods

Because the present study was a retrospective analysis, formal estimation of the sample size and calculation of the power were not performed. The Fisher's exact test was used to calculate the *P* value for the association between patient characteristics, K-ras mutations, skin toxicity, and disease control rate of treatment.

Progression-free survival (PFS) was calculated from the start of the study treatment to the date of progression or last follow-up. OS was calculated from the first day of the study treatment to the day of death or last follow-up. Both PFS and OS were estimated using the Kaplan–Meier method and compared using the log-rank test. Multivariate analysis using the Cox proportional hazards model was used to estimate the simultaneous effects of prognostic factors for survival. The differences were considered to be statistically significant when $P \leq 0.05$.

Results

Patient characteristics

Patient characteristics are summarized in Table 1. There were 18 (56%) males and 14 (44%) females, and the median age of the patients was 52 years (range 28–82 years). Seventeen (53%) patients had an Eastern Cooperative Oncology Group (ECOG) performance status of 2 or 3, and most

patients (81%) had multiple metastases involving two or more organ systems. Patients were heavily pretreated with a median number of three previous lines of palliative chemotherapy (range 1–6) (Table 1). Eighteen patients (56%) had been previously exposed to all of the following classes of drugs: fluoropyrimidines, cisplatin, irinotecan, oxaliplatin, and docetaxel. All patients had been refractory to prior chemotherapy, which was defined as progression while receiving chemotherapy.

K-ras mutation

Sequencing of K-ras codons 12 and 13 was performed in 30 patients, among whom 4 patients (13.3%) displayed a K-ras mutation: G12D ($n = 1$) and G12V ($n = 1$) at codon 12, G13C ($n = 1$) and G13V ($n = 1$) at codon 13. Among three patients in whom tumor samples were available from both primary gastric tumor site and metastatic site, two patients had the same K-ras mutation status between two sites and one patient showed the discordant result.

Treatment administration

Median number of chemotherapy cycle was 2 (range 1–7) and the median week of cetuximab treatment was 6 weeks (range 1–28). Median dose intensity of cetuximab, irinotecan, oxaliplatin, and docetaxel was 1.00 (range 0.97–1.00), 0.91 (range 0.50–1.00), 0.98 (range 0.94–1.00), and 0.97 (range 0.95–1.00), respectively.

Response

Of the 32 patients, 28 were assessed for tumor response. Four patients could not be assessed for overall response rate because one patient died as a result of asphyxia during week 2 of treatment and three patients refused treatment after just 1 week ($n = 1$) or 2 weeks of treatment ($n = 2$). One patient (3.6%) achieved a partial response, 7 patients (25.0%) displayed stable disease, and 20 patients (71.5%) experienced disease progression. The overall response rate was 3.6% (95% CI 0–10.5%), and the disease control rate (partial response plus stable disease) was 28.6%. When the differences in disease control rate were evaluated by patient characteristics, prior therapy, and the type of chemotherapy administered concomitantly with cetuximab, there was a significant difference in the disease control rate based on ECOG performance status (1 vs. ≥ 2 , 53.8 vs. 6.7%; $P = 0.01$) (Table 2). An acne-like skin rash was observed in 50% of the patients, among whom 11 (34%) presented a grade 1 rash and 5 (16%) presented a grade 2 skin rash. Skin rash was also significantly associated with the disease control rate (grade 0–1 vs. 2, 17.4 vs. 80.0%; $P = 0.01$). K-ras mutation, however, was not associated with the

Table 1 Patient characteristics ($N = 32$)

Characteristics	No. of patients
Sex	
Male	18 (56%)
Female	14 (44%)
Median age (range)	52 (28–82)
ECOG performance status	
1	15 (47%)
2	13 (41%)
3	4 (12%)
Histology	
Papillary cell carcinoma	1 (3%)
Well-differentiated adenocarcinoma	3 (9%)
Moderately differentiated adenocarcinoma	7 (22%)
Poorly differentiated adenocarcinoma	12 (38%)
Signet ring cell carcinoma	9 (28%)
Metastatic organ site	
Peritoneum	20 (63%)
Abdominal distant lymph node	14 (44%)
Liver	12 (38%)
Ureter	9 (28%)
Others	25 (78%)
No. of metastatic organ sites	
1	6 (19%)
2	13 (41%)
≥ 3	13 (41%)
Prior surgery	
Total gastrectomy	8 (25%)
Subtotal gastrectomy	7 (22%)
Prior adjuvant chemotherapy	
Docetaxel + cisplatin	4 (13%)
5-Fluorouracil or tegafur/uracil \pm mitomycin C	4 (13%)
5-Fluorouracil + cisplatin or epirubicin	3 (9%)
Capecitabine	1 (3%)
No. of previous regimens ^a	
1	3 (9%)
2	8 (25%)
≥ 3	21 (66%)
Previous agent exposure ^a	
Fluoropyrimidines	32 (100%)
Cisplatin	29 (91%)
Irinotecan	27 (84%)
Oxaliplatin	27 (84%)
Docetaxel	25 (78%)
Others ^b	10 (31%)
Best response to most recent chemotherapy	
Partial response	2 (6%)
Stable disease	11 (34%)
Progressive disease	19 (59%)

ECOG Eastern Cooperative Oncology Group

^a Excluding adjuvant therapy^b Including epirubicin, methotrexate, mitomycin C, or bevacizumab**Table 2** Differences in disease control according to patient characteristics

	Disease control rate (%)	P value ^a
Age		
<60 years ($n = 23$)	34.8	0.28
≥ 60 years ($n = 5$)	0	
ECOG performance status		
1 ($n = 13$)	53.8	0.01
≥ 2 ($n = 15$)	6.7	
Differentiation		
Differentiated ($n = 9$)	22.2	1.00
Undifferentiated ($n = 19$)	31.6	
No. of metastatic organ sites		
<3 ($n = 16$)	43.8	0.08
≥ 3 ($n = 12$)	8.3	
No. of prior chemotherapies		
<3 ($n = 8$)	37.5	0.65
≥ 3 ($n = 20$)	25.0	
Best response to most recent chemotherapy		
PR + SD ($n = 11$)	27.3	1.00
PD ($n = 17$)	29.4	
Chemotherapy administered with cetuximab		
Irinotecan-based ($n = 25$)	28.0	1.00
Non-irinotecan-based ($n = 3$)	33.3	
K-ras mutation		
Wild-type ($n = 22$)	31.8	1.00
Mutant ($n = 4$)	25.0	
Skin rash		
Grade 0–1 ($n = 23$)	17.4	0.01
Grade 2 ($n = 5$)	80.0	

ECOG Eastern Cooperative Oncology Group, PR partial response, SD stable disease, PD progressive disease

^a Fisher's exact testdisease control rate (wild-type vs. mutant, 36.8 vs. 25.0%; $P = 1.00$).

Survival

All 32 patients were evaluated for survival analysis. The median duration of follow-up was 18.8 months (range 7.0–30.4 months). The median PFS was 1.7 months (95% CI 1.3–2.1 months), and the median OS was 3.2 months (95% CI 1.4–5.0 months) (Fig. 1).

Univariate Cox regression analysis revealed that the ECOG performance status and skin rash were statistically significant factors influencing PFS (Table 3). The median PFS was 1.4 months in patients with poor performance status (ECOG performance status ≥ 2), as compared with 2.4 months in those with good performance status (log-rank

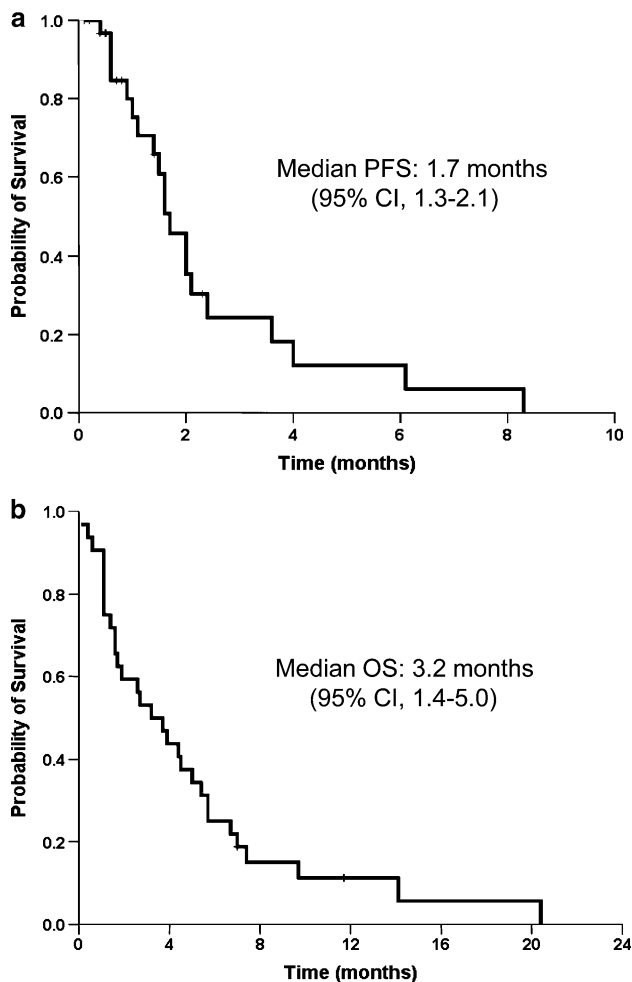


Fig. 1 Progression-free survival (a) and overall survival (b) among all patients ($n = 32$)

$P = 0.002$) (Fig. 2a). The median PFS of patients with skin rash grade 0 versus grade 1 versus grade 2 was 1.0 versus 1.7 versus 4.0 months, respectively (log-rank $P < 0.001$) (Fig. 2b).

Multivariate analysis showed that lack of skin rash [hazard ratio (HR) = 5.03; 95% CI 1.29–19.70; $P = 0.02$] was a significant independent prognostic factor for PFS, and poor ECOG performance status demonstrated only borderline significance (HR = 3.36; 95% CI 0.96–11.79; $P = 0.05$) (Table 3).

With regard to OS, univariate and multivariate analyses revealed that ECOG performance status (HR = 5.49; 95% CI 2.08–14.50; $P = 0.001$), the number of metastatic organ sites (HR = 5.68; 95% CI 2.23–14.48; $P < 0.001$), and skin rash (HR = 6.00; 95% CI 2.34–15.38; $P < 0.001$) were significant independent prognostic factors (Table 4; Fig. 2c, d).

In a combined analysis of ECOG performance status and skin rash, patients with two favorable prognostic factors (the presence of skin rash and good performance status) had

a median PFS of 3.6 months (95% CI 1.6–5.6 months) and OS of 5.7 months (95% CI 4.0–7.3 months), compared with 1.1 months (95% CI 0.5–1.7 months) (HR = 9.9; 95% CI 2.61–37.91; $P = 0.001$) and 1.6 months (95% CI 1.0–2.2 months) (HR = 3.62; 95% CI 1.49–8.75; $P = 0.004$) for patients with only one favorable prognostic factor (the presence of skin rash or good performance status) or no favorable prognostic factors (Fig. 3). The presence of a K-ras mutation was not associated with either PFS or OS.

Discussion

Here, we have shown that cetuximab plus mainly irinotecan-based chemotherapy resulted in a 3.6% response rate, 28.6% disease control rate, 1.7 months of median PFS, and 3.2 months of median OS in heavily pretreated MGC patients. Given that most of our patient cohort (91%) had failed two or more prior regimens, that more than 50% of the patients had been refractory to nearly all effective agents including fluoropyrimidines, cisplatin, irinotecan, oxaliplatin, and docetaxel, and that more than 50% of the patients had poor performance status, these results suggest the possible role of cetuximab combined with other chemotherapies as a salvage therapy in these patients. Recently, several phase II trials showed that cetuximab plus chemotherapy, including oxaliplatin/5-FU/LV, irinotecan/5-FU/LV, capecitabine/cisplatin or oxaliplatin, 5-FU/LV/cisplatin, or oxaliplatin/irinotecan, resulted in a 48.1–68.6% response rate, 5.23–8 months of median time to progression, and 9.5–16 months of median OS in locally advanced or MGC patients as a first-line treatment [25–32]. As a second-line therapy, cetuximab plus docetaxel resulted in a 6% response rate, 2.1 months of median PFS, and 5.3 months of median OS [35].

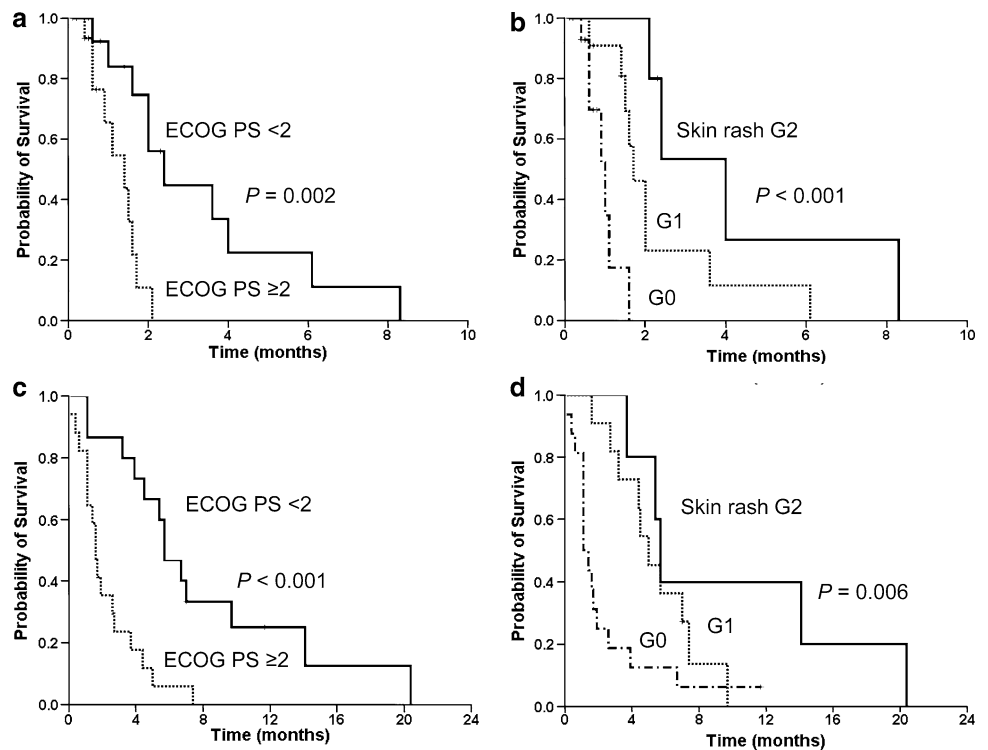
Because of the high cost and inconvenience of weekly doctor visits for treatment, it is necessary to better define the subpopulation of patients who have the highest chance of benefiting from cetuximab. This goal would likely be more important in the salvage setting when considering possible treatment-related toxicities in heavily pretreated patients. Although the present study comprised a small sample size, our analysis showed that ECOG performance status and skin rash were associated with the disease control rate, PFS, and OS in MGC patients treated with cetuximab combined with chemotherapy in a salvage setting. Patients with good performance status and a skin rash demonstrated better PFS (median PFS 3.6 vs. 1.1 months; $P < 0.001$) and OS (median OS 5.7 vs. 1.6 months; $P = 0.002$) than those with poor performance status and/or lack of skin rash. Skin rash appears to be a surrogate marker for cetuximab efficacy regardless of the type of cancer or nature of administration (first-line or salvage)

Table 3 Cox regression analysis of prognostic factors for progression-free survival

	Univariate analysis			Multivariate analysis		
	HR	95% CI	<i>P</i> value	HR	95% CI	<i>P</i> value
Age \geq 60 years vs. <60	1.69	0.54–5.33	0.37	–	–	–
Female vs. male	1.43	0.57–3.60	0.44	–	–	–
ECOG PS \geq 2 vs. 1	5.11	1.65–15.82	0.005	3.36	0.96–11.79	0.05
Undifferentiated vs. differentiated	1.02	0.40–2.61	0.96	–	–	–
No. of metastatic organ sites \geq 3 vs. <3	1.73	0.65–4.61	0.27	–	–	–
No. of prior chemotherapies \geq 3 vs. <3	0.87	0.31–2.44	0.79	–	–	–
Best response to most recent chemotherapy, PD vs. PR + SD	0.66	0.25–1.76	0.41	–	–	–
Chemotherapy given with cetuximab, non-irinotecan-based vs. irinotecan-based	1.15	0.33–4.06	0.83	–	–	–
K-ras mutant vs. wild-type	0.38	0.05–2.94	0.35	–	–	–
Skin rash G0 vs. $G \geq$ 1	8.99	2.40–33.72	0.001	5.03	1.29–19.70	0.02

HR hazard ratio, CI confidence interval, ECOG Eastern Cooperative Oncology Group, PR partial response, SD stable disease, PD progressive disease, *G* grade

Fig. 2 Progression-free survival (a, b) and overall survival (c, d) according to the Eastern Cooperative Oncology Group (ECOG) performance status (PS) and skin rash grade



[19, 20, 32, 36, 37]. Although the mechanism underlying the correlation between skin toxicity and treatment efficacy of cetuximab is currently unclear, it has been hypothesized that the rash may reflect the extent of EGFR blockade in both patients and tumors and that it may reflect the patients' ability to develop an inflammatory reaction in response to cellular damage caused by EGFR inhibition in the skin. Consequently, patients in whom EGFR blockade is able to trigger an inflammatory response might be more likely to develop rash irrespective of the degree of EGFR inhibition in the tumor [38].

Mutation of K-ras which is a predictive factor for cetuximab efficacy in colorectal cancer was found in 13.3% of the analyzed tumors, consistent with previously reported results in gastric cancer, which ranged from 2.8 to 21% [39–43]. These frequencies of K-ras mutations in gastric cancer are lower than those in colorectal cancer, which are about 40% [44]. In contrast to previous results in colorectal cancer [21, 22, 24], K-ras mutation status was not associated with cetuximab treatment efficacy in the present study. This is consistent with the report by Stella et al. [45] stating that K-ras mutation was not associated with the tumor

Table 4 Cox regression analysis of prognostic factors for overall survival

	Univariate analysis			Multivariate analysis		
	HR	95% CI	<i>P</i> value	HR	95% CI	<i>P</i> value
Age \geq 60 years vs. <60	1.86	0.74–4.67	0.19	–	–	–
Female vs. male	1.42	0.68–2.98	0.35	–	–	–
ECOG PS \geq 2 vs. 1	4.40	1.90–10.17	0.001	5.49	2.08–14.50	0.001
Undifferentiated vs. differentiated	1.35	0.61–2.98	0.45	–	–	–
No. of metastatic organ sites \geq 3 vs. <3	3.72	1.61–8.59	0.002	5.68	2.23–14.48	<0.001
No. of prior chemotherapies \geq 3 vs. <3	1.14	0.51–2.53	0.75	–	–	–
Best response to most recent chemotherapy, PD vs. PR + SD	1.45	0.67–3.15	0.34	–	–	–
Chemotherapy given with cetuximab, non-irinotecan-based vs. irinotecan-based	1.05	0.36–3.07	0.92	–	–	–
K-ras mutant vs. wild-type	0.86	0.26–2.89	0.80	–	–	–
Skin rash G0 vs. G \geq 1	3.16	1.46–6.85	0.004	6.00	2.34–15.38	<0.001

HR hazard ratio, CI confidence interval, ECOG Eastern Cooperative Oncology Group, PR partial response, SD stable disease, PD progressive disease, G grade

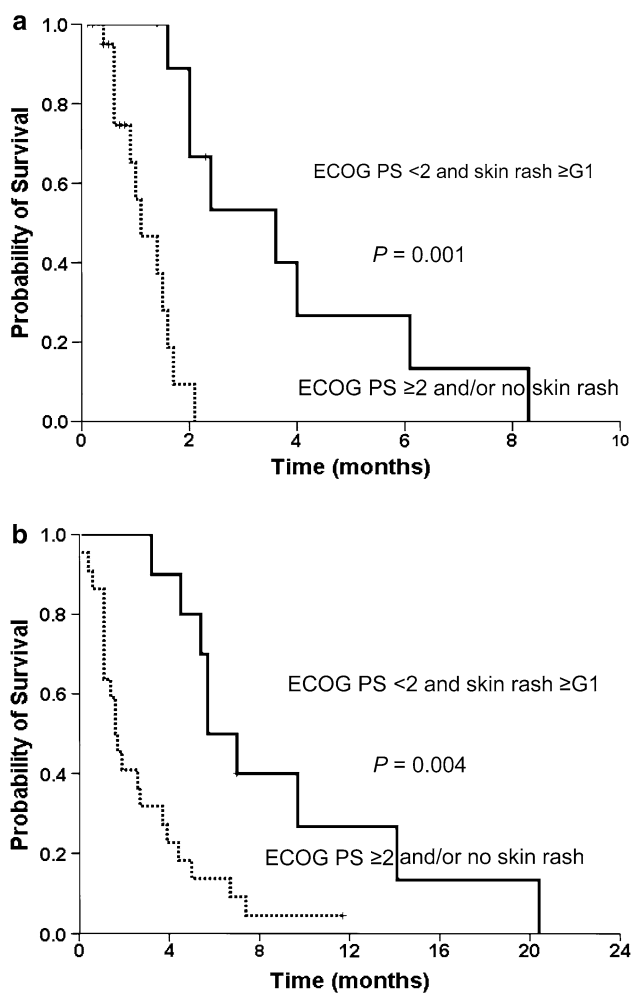


Fig. 3 Progression-free survival (a) and overall survival (b) according to favorable prognostic factors (the presence of skin rash and good performance status)

response to cetuximab plus chemotherapy as a first-line treatment in 43 patients with locally advanced or MGC. It is possible that, in gastric cancer, the molecular mechanisms of resistance to cetuximab can be attributed to other process such as the activation of alternative tyrosine kinase receptors that bypass the EGFR pathway (e.g., IGF-1R and c-Met) rather than RAS constitutive activation by K-ras mutation. Recently, serum EGFR ligands were reported to be implicated in responsiveness to cetuximab therapy in gastric cancer [32]. However, the absence of an association between K-ras mutations and treatment efficacy with cetuximab may be a result of the small sample size. In addition, the low incidence of K-ras mutation in gastric cancer may also contribute to the lack of a significant association with therapeutic success. Thus, this result does not absolutely exclude K-ras mutations as a predictive factor for cetuximab efficacy in gastric cancer, but suggests that, in the clinical setting, the role of K-ras mutation status as a marker for selection of patients who are likely to benefit from cetuximab is less useful than in other types of cancer that harbor a higher K-ras mutation frequency, such as colorectal cancer.

To our knowledge, this is the first study to examine the treatment efficacy of cetuximab combined with chemotherapy in the salvage setting for MGC patients and to correlate treatment success with other factors such as skin rash, ECOG performance status, and K-ras mutation status.

In conclusion, our study suggests that MGC patients with good performance status and skin rash may benefit the most from cetuximab combined with other chemotherapy despite being refractory to nearly all effective chemotherapy. A decision whether starting and/or continuing cetuximab with chemotherapy in these patients could be based

on performance status as a prognostic factor in advanced gastric cancer and skin rash during early treatment period as a predictive factor. Large-scale prospective studies are needed to confirm these findings.

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Conflict of interest statement None.

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