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ORIGINAL ARTICLE

Second-line panitumumab as a triweekly dose for patients with wild-type *KRAS* exon 2 metastatic colorectal cancer: a single-institution experience

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ABSTRACT

Objective: Panitumumab administered as monotherapy in colorectal cancer (CRC) has shown response and disease stabilization rates of approximately 30%. The current study aimed to evaluate the progression-free survival (PFS) and overall survival (OS) of patients with metastatic colorectal cancer (mCRC) treated with panitumumab every 3 weeks as a second line treatment.

Methods: This study is a retrospective analysis of 18 patients, aged more than 18 years, with wild-type *KRAS* exon 2 mCRC treated with panitumumab as a second-line single agent after progression on first-line chemotherapy.

Results: The median number of courses received was 10 (range, 4-29), and the median duration of treatment was 30 weeks (range, 12-96 weeks). After a median follow-up period of 13 months, the median PFS was 6 months (range, 4.3-7.7 months) and the median OS was 11 months (range, 7.4-14.5 months). The median PFS was 4 months for patients with < grade 2 skin toxicity and 6 months (range, 4.5-7.5 months) for patients with ≥ grade 2 skin rash (P=0.05). The median OS was 9 months (range, 6.4-11.5 months) and 14 months (range, 11.6-16.3 months) for the two groups of patients (P=0.002).

Conclusions: Panitumumab given every 3 weeks is effective and well tolerated in patients with advanced CRC that progressed after standard chemotherapy.

KEYWORDS Metastatic colorectal carcinoma; panitumumab; second-line; *KRAS*

Introduction

Colorectal cancer (CRC) is a malignant neoplasm originating in the lower part of the digestive system, including the colon and rectum. In metastatic colorectal cancer (mCRC), the tumor spreads beyond the local or regional lymph nodes to other parts of the body, such as the liver, lungs, peritoneum, and para-aortic lymph nodes (stage IV disease). At the time of diagnosis, an estimated 20%-55% of people with CRC already have metastatic disease. Moreover, approximately 50%-60% of the people who have undergone surgery for early-stage CRC will eventually develop metastatic disease, most commonly in the liver[1].

The management of mCRC is mainly palliative, and includes combinations of treatment modalities, such as palliative surgery, chemotherapy, and radiation, for symptom control and psychosocial support. However, approximately 8% of people with mCRC have potentially resectable liver metastases, and chemotherapy may render these liver metastases operable[2]. Epidermal growth factor receptor (EGFR) has been validated as a therapeutic target in several human tumors, including CRC[3-6]. Ligand occupancy of EGFR activates the RAS/RAF/MAPK, STAT, and PI3K/AKT signaling pathways, which modulate cellular proliferation, adhesion, angiogenesis, migration, and survival[7,8]. The antiEGFR targeted antibodies cetuximab and panitumumab, administered as monotherapy in CRC, have shown response and disease stabilization rates of approximately 10% and 30%, respectively[4,5].

Retrospective studies have identified *KRAS* mutation in tumors as a negative predictive factor for panitumumab and cetuximab for improved response rate (RR), progression-free survival (PFS), and overall survival (OS)[9-15]. In September 2007, a prospectively defined retrospective analysis of the pivotal phase III study of panitumumab as monotherapy in mCRC setting provided evidence that clinical benefits are specific to patients with wildtype (WT) *KRAS* tumors[16]. Panitumumab can be administered from a weekly to a triweekly schedule. In a dose-finding study, panitumumab, given at a dose of 9 mg/kg triweekly, was well tolerated and

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exhibited predictable pharmacokinetics with low intra- and inter-patient variability[17].

The current study aimed to evaluate the PFS and OS for mCRC patients treated with panitumumab every 3 weeks as second-line treatment.

Patients and methods

This study included 18 patients aged more than 18 years, both males and females, with WT *KRAS* axon 2 mCRC treated by panitumumab as a second-line single agent after progression on first-line chemotherapy, during the period of January 2007 to December 2012. This study was approved by the Institutional Review Board at Mansoura Faculty of Medicine, King Abdullah Medical City. Written informed consent was obtained from all patients for the publication of this study.

Patient's criteria

The studied patients had no previous anti-EGFR therapy, antitumor therapy within 30 days, symptomatic brain metastases needing treatment, significant cardiovascular disease, history of interstitial lung disease, serum magnesium concentrations below the lower normal limit, inadequate hematological function, inadequate renal function, or inadequate hepatic function.

Treatment

Panitumumab (Vectibix, Amgen) was administered at a dose of 9 mg/kg over 60 min by intravenous infusion. Treatment was given every 21 days until disease progression, unacceptable toxicity, or withdrawal of the patient.

KRAS testing

We assessed the *KRAS* tumor status in formalin-fixed, paraffin-embedded tumor tissue sections for the presence or absence of the seven most common *KRAS* mutations. Exon 2 mutations were assessed with Thera screen *KRAS* assay (Biomnis, Lyon, France). Other *RAS* and *BRAF* mutation tests were not performed in this group of patients. All *RAS* tests are part of the standard therapy before administering panitumumab.

Assessment

The data collected included performance status, histopathology, abdominopelvic MRI/CT, chest CT, *KRAS* status, type of prior surgery, number of involved organs and locations, prior chemotherapy received, chemotherapy regimen used and number of cycles received, and panitumumab doses and number of cycles received. Clinical response and its duration were assessed according to the response evaluation criteria in solid tumors (RECIST) guidelines. Data for assessment of the treatment related toxicity and its degree were collected. Adverse events (AEs) were graded using the Common Terminology Criteria for AEs (version 4.0)[18].

Outcomes

Analysis included measurement of PFS and OS of the treated patients. PFS was defined as the length of time during and after treatment, in which the disease did not worsen. Survival was defined as the time from the start of treatment with panitumumab until death (patients lost from follow up were censored at the time they were last determined to be alive).

Statistical analysis

SPSS software version 21.0 was used for statistical analysis. The primary objective of this study was to evaluate the PFS. The Kaplan-Meier method was used to analyze the time to an event, such as median time to progression, duration of response, PFS, and OS. Variables were described using mean, median, minimum, and maximum values. Analysis of treatment efficacy based on grade of skin rash toxicity was also performed using log-rank test for PFS and OS. Correlation analysis between the grade of skin rash and response was also conducted using Pearson Chi-square test.

Results

The study included 18 patients with WT *KRAS* mCRC. Their median age was 53 years (range, 36-72 years), with male to female ratio of 2:1 (**Table 1**). Patients with performance status of 0-1 represented 83% of the studied group. All patients had previous surgery: radical (28%), palliative (61%), or both (11%). First-line chemotherapy was given to all patients before panitumumab treatment. Approximately 44% of patients received oxaliplatin-based chemotherapy as first-line treatment, whereas 56% received irinotecan-based chemotherapy. Bevacizumab was given to 50% of patients.

All patients received four cycles or more of triweekly panitumumab. The median number of courses received was 10 (range, 4-29) with a median treatment duration of 30

Table 1 Patient's characteristics

Characteristics	*n*	%
Age, years		
Median	53	
Range	36-72	
Gender		
Males	12	67
Females	6	33
Tumor grade		
Grade 1	1	6
Grade 2	11	61
Grade 3	6	33
Performance status (ECOG)		
0	4	22
1	5	28
2	6	33
3	3	17
Type of previous surgery		
Curative	5	28
Palliative	11	61
Both (curative/palliative)	2	11
Type of previous chemotherapy regimen (first line)		
Oxaliplatin-based chemotherapy	8	44
Irinotecan-based chemotherapy	10	56
Number of involved organs		
1	7	39
2	8	44
≥3	3	17
Sites affected		
Liver	9	50
Lung	7	39
Peritoneal	2	11
Lymph nodes	6	33

weeks (range,12-96 weeks). Panitumumab was administered to all patients at a dose of 9 mg/kg. However, treatment was delayed in 5 patients (28%) because of deterioration of general conditions, especially in elderly patients, leucopenia, or anemia requiring supportive measures. Treatment was discontinued in 11 patients (61%) because of disease progression, 2 patients because of development of grade 4 skin toxicity and refusal to continue treatment (11%), and 3 patients (17%) because of death or loss to follow up.

Four patients (22%) showed partial response, whereas disease stabilization was achieved in 8 patients (44%) (**Table 2**). The median time to response for patients who achieved partial response was 4.7 months (range, 4.2-5.5 months), whereas the median duration of the obtained response was 6 months (range, 4.3-7.7 months). After a median follow-up period of 13 months, the median PFS was 6 months (range, 4.3-7.7 months) and the median OS was 11 months (range, 7.4-14.5 months).

The association between the degree of skin toxicity and the obtained clinical response showed that four patients (100%) among those who obtained partial response and six patients (75%) with stationary disease had ≥ grade 2 skin toxicity out of the 11 patients with ≥ grade 2 skin toxicity. Meanwhile, two patients (25%) among the 7 patients with < grade 2 skin toxicity had stationary disease (P=0.02) (**Table 3**).

For patients with grade 2 skin toxicity, the median PFS was 4 and 6 months (range, 4.5-7.5 months) for patients with ≥ grade 2 skin rash (P=0.05). The median OS was 9 months (range, 6.4-11.5 months) and 14 months (range, 11.6-16.3 months) for the two groups of patients (P=0.002).

Hypomagnesemia was reported in 2 patients (11%) among the 8 patients (44%) with grade 3 toxicity. The degree of hypomagnesemia was associated with the obtained clinical response. Three patients (75%) among those who obtained a partial response and two patients (100%) with stationary disease had ≥ grade 2 hypomagnesemia out of the six patients

Table 2 Response assessment

Items	*n*	%
Complete response	0	0
Partial response	4	22.2
Stable disease	8	44.4
Progressive disease	6	33.4
Total	18	100.0

Table 3 Response assessment in relation to skin

Items	Degree of skin rash		Total
	<Grade 2, *n* (%)	≥ Grade 2, *n* (%)	
Complete response	0	0	0
Partial response	0	4 (100)	4 (100.0)
Stationary course	2 (25)	6 (75)	8 (100.0)
Progressive disease	5 (83)	1 (17)	6 (100.0)
Total	7 (39)	11 (61)	18 (100.0)

with ≥ grade 2 hypomagnesemia. Meanwhile, one patient out of the two with < grade 2 hypomagnesemia had partial response (P=0.51) (**Table 4**).

The treatment-related toxicities are shown in **Table 5**. Skin rash was the most frequent toxicity among the treated patients (13 patients, 73%), followed by diarrhea (9 patients, 50%). Only one patient developed grade 3 diarrhea requiring hospitalization. Two patients (11%) stopped panitumumab treatment because of the development of a grade 4 skin rash.

Discussion

The findings of this study indicated that panitumumab monotherapy given every 21 days was well tolerated and effective in mCRC patients with disease progression after standard chemotherapy.

The RR observed in this study (22%) was better than the previously reported RRs of 8.5%-11.6% in irinotecan and oxaliplatin refractory patients treated with either cetuximab or panitumumab monotherapy[19-21]. This result could be attributed to the fact that testing of the K-RAS status was not conducted for patients in these studies before starting treatment, as well as the small sample size of our study. In a Japanese single-institution study, the RR was 12.5%, and all patients with WT K-RAS achieved a partial response[21]. In a group of patients with WT K-RAS treated with panitumumab as a single agent after progression on both oxaliplatin and irinotecan, the RR was 17%[16]. These results indicated the value of testing the K-RAS status before giving panitumumab as response to treatment was affected by the K-RAS status. In a recent phase III study (ASPECCT) comparing cetuximab and panitumumab based on WT-KRAS exon 2 testing for patients with mCRC refractory to chemotherapy, the RR for the group that received panitumumab was 22%, which was the same as in our study[22]. In the PRIME study[23], Oliner and colleagues demonstrated through biomarker analysis, including K-RAS, N-RAS, and BRAF, that patients with any RAS mutation or a BRAF mutation had worse PFS and worse OS when treated with panitumumab combined with FOLFOX4. By contrast, patients with WT K-RAS exon 2 tumors were associated with a 5.8-month improvement in OS (hazard ratio =0.78; 95% CI, 0.62-0.99; P=0.043).

The median PFS and median OS were 6 and 11 months, respectively. These findings were better than those of a previous study comparing panitumumab and best supportive care without testing K-RAS, with 2.5 and 6.3 months, respectively[5]. In a phase 3 randomized, controlled multicenter study comparing panitumumab in WT K-RAS mCRC *vs*. BSC for mutant K-RAS mCRC patients, the OS was 8.1 *vs*. 4.4 months, respectively[24]. In the ASPECCT study for patients treated with panitumumab, the PFS and OS were 4.1 and 10.4 months, respectively, similar to our findings.

Table 4 Response assessment in relation to hypomagnesaemia

Items	Degree of hypomagnesaemia		Total
	<Grade 2, *n* (%)	≥ Grade 2, *n* (%)	
Complete response	0 (0)	0 (0)	0 (0)
Partial response	1 (25)	3 (75)	4 (100.0)
Stationary course	0 (0)	2 (100)	2 (100.0)
Progressive disease	1 (50)	1 (50)	2 (100.0)
Total	2 (25)	6 (75)	8 (100.0)

Table 5 Treatment related toxicity (18 patients)

Items	Grade 1, *n* (%)	Grade 2, *n* (%)	Grade 3, *n* (%)	Grade 4, *n* (%)	Overall, *n* (%)
Skin dryness	1 (5.6)	2 (11.2)	2 (11.2)	0	5 (28)
Skin fissures	1 (5.6)	0	0	0	1 (5.6)
Skin rash	2 (11.2)	8 (44.8)	1 (5.6)	2 (11.2)	13 (72.8)
Stomatitis	1 (5.6)	3 (16.8)	1 (5.6)	0	5 (28)
Anorexia	3 (16.8)	1 (5.6)	0	0	4 (22.4)
Vomiting	3 (16.8)	2 (11.2)	0	0	5 (28)
Diarrhea	2 (11.2)	6 (33.6)	1 (5.6)	0	9 (50)
Neutropenia	1 (5.6)	2 (11.2)	1 (5.6)	0	4 (22.4)
Alopecia	3 (16.8)	1 (5.6)	1 (5.6)	0	5 (28)
Asthenia	2 (11.2)	4 (22.4)	0	0	6 (33.6)
Hypomagnesaemia	2 (11.2)	4 (22.4)	2 (11.2)	0	8 (44.8)

This relatively high rate of PFS and OS could be attributed to previous treatment with bevacizumab in about 50% of our patients prior to their entry into the study. This finding was also reported in the ASPECCT study, but no biological explanation was provided.

Skin rash is a characteristic toxicity of panitumumab and other EGFR inhibitors. Consistent with previous reports, we found an association between clinical efficacy and rash severity[5,23]. The incidence of skin toxicity in panitumumab-treated patients was dose related, but we did not observe a correlation between dose and severity. The time to the worst grade of rash did not differ from the time to any other grade of rash[10-15].

Although skin rash appears to be a marker of drug activity associated with clinical benefit, it also often develops in patients who do not benefit from treatment. Hypomagnesemia occurred in 44% of patients, with its peak after three to four months. In most instances, hypomagnesemia was managed by the treating physician, and it was not a cause to withhold or change the dose of panitumumab. We noted an association between the grade of hypomagnesemia and the RR, but without statistical significance (P=0.51). In a recent Japanese study, hypomagnesemia was observed more commonly in patients exposed to long treatment period with EGFR inhibitors[25]. Consistent with the fully human monoclonal antibody nature of panitumumab, we observed a low incidence of infusion reactions.

In conclusion, this study demonstrated that panitumumab given every 3 weeks was effective and well tolerated in patients with advanced CRC that had progressed after standard chemotherapy. Panitumumab represents a novel treatment option that can improve PFS with manageable toxicity in patients with chemorefractory mCRC. However, further comparative randomized studies are necessary to reach firm conclusions based on both clinical and pharmacological bases.

Conflict of interest statement

No potential conflicts of interest are disclosed.

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