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ORIGINAL ARTICLE

A real-life experience using panitumumab in chemo-refractory metastatic colorectal cancer patients: a retrospective analysis at the Jewish General Hospital, 2009–2012

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ABSTRACT

Background

Panitumumab is a fully human monoclonal antibody, directed against the epidermal growth factor receptor, that was shown to be effective in third-line metastatic colorectal cancer. We performed a retrospective analysis of patients with chemo-refractory non-*KRAS*-mutated metastatic colorectal cancer, who received panitumumab at the Jewish General Hospital in Montreal, Canada, between 2009 and 2012.

Methods

This chart review included 44 patients (median age: 60 years; performance status: 0–3), of whom 50% had already received three lines of treatment. The primary endpoint was progression-free survival (PFS). Secondary endpoints were overall survival and safety. Tumour progression was determined by radiologic assessments performed once every 3 months per clinical guidelines or by clinical deterioration as determined by the clinician–investigator.

Results

In our sample, median PFS was 21.86 ± 5.23 weeks (95% confidence interval: 12.9 to 36.9 weeks) and overall survival was 35.14 ± 7.75 weeks (95% confidence interval: 25.6 to 73.4 weeks) with a median of 5 cycles of panitumumab treatment. The most frequently reported toxicities with panitumumab were skin toxicity (16.2% grade 3) and hypomagnesemia (10.8% grade 3). No infusion reactions were reported.

Conclusions

Despite a small sample size from a single institution, our survival and efficacy data are encouraging and comparable to results obtained from the registration panitumumab trial. Our findings suggest that panitumumab can be effective and tolerable in a real-world setting.

KEY WORDS

Metastatic colorectal cancer, panitumumab, progression-free survival, overall survival, safety

1. INTRODUCTION

Panitumumab (Vectibix: Amgen, Thousand Oaks, CA, U.S.A.) is a fully human monoclonal antibody directed against the epidermal growth factor receptor (EGFR)[1–4]. Panitumumab binds to EGFR and prevents receptor dimerization, autophosphorylation, and activation of downstream signalling pathways responsible for cellular proliferation and tumour growth[5,6]. The drug has been studied as monotherapy and in combination with irinotecan, oxaliplatin, and 5-fluorouracil–based chemotherapy in various lines of metastatic colorectal cancer (mCRC) treatment[7,8].

In third-line treatment, cetuximab, a chimeric monoclonal anti-EGFR antibody was shown to be active and well tolerated in colorectal cancer patients[9–14]. To evaluate the effectiveness of panitumumab, a randomized phase III trial was designed in which 463 patients were randomly assigned to the study drug (6 mg/kg every 2 weeks) plus best supportive care (BSC) or to BSC alone. Results showed a statistically significant and clinically meaningful improvement in mean progression-free survival (PFS) in the group receiving panitumumab compared with the group receiving BSC alone (13.8 weeks vs. 8.5 weeks, $p < 0.0001$). However, no difference in overall survival (OS) was observed, a finding that was attributed to the effects of panitumumab in the BSC group after the preplanned crossover[7].

Recently, the predictive role of *KRAS* was explored in patients receiving anti-EGFR therapies[15–22]. Results showed that 35%–45% of patients with mCRC harbour mutations in the *KRAS* gene and do not benefit from anti-EGFR therapies. A follow-up study

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conducted by Amado *et al.*[22] showed that the effect of panitumumab on PFS was significantly greater in patients with wild-type *KRAS* than in those with the mutated gene ($p < 0.0001$). Overall survival was also longer in patients with wild-type *KRAS* [hazard ratio: 0.67; 95% confidence interval (CI): 0.55 to 0.82]. As a result of those studies, *KRAS* status is now required before initiating anti-EGFR treatment.

We performed a retrospective chart review and examined PFS, OS, and safety in MCRC patients with non-mutated *KRAS,* who failed all lines of chemotherapy and who received panitumumab as palliative treatment at the Segal Cancer Centre of the Jewish General Hospital in Montreal, Quebec, Canada.

2. METHODS

2.1 Patient Population

Patients more than 18 years of age with MCRC and documented evidence of failure of fluoropyrimidines, oxaliplatin, and irinotecan were eligible for panitumumab treatment between July 2009 and March 2012. They received either panitumumab 6 mg/kg every 2 weeks or the same dose of panitumumab plus irinotecan 180 mg/m^2 according to the treating physician's choice until disease progression or unacceptable toxicity. Treatment with panitumumab with or without irinotecan was defined as receiving at least 1 infusion. In these patients, *KRAS* status was determined by polymerase chain reaction and sequencing at the Jewish General Hospital. Patients who had a mutated *KRAS* gene or who had previously been treated with cetuximab were excluded from the study. Because the present review was intended as a good clinical practice report, it did not require submission to the Research Ethics Board.

2.2 Statistical Analysis

The primary endpoint of the study was PFS, defined as the interval from treatment assignment to progression or death. Two survival outcomes were recorded:

- Tumour progression
  Progression was determined using the Response Evaluation Criteria in Solid Tumors (version 1.1) or clinical deterioration as documented by the treating clinician. Patients underwent computed tomography imaging every 3 months per standard clinical guidelines for tumour assessments or to confirm suspected clinical deterioration (clinician's choice). Tumour response was assessed by the treating physician, who documented it in the medical chart.

- Death
  Date of death was captured from patient charts.

Secondary endpoints included OS and safety. Adverse events attributable to panitumumab treatment were reported and graded by the treating physician in the chart during a medical visit. The grading of toxicities was based on safety guidelines per the *Common Terminology Criteria for Adverse Events,* version 4.0.

The statistical analysis was performed using the Strata 10 software application (StataCorp LP, College Station, TX, U.S.A.). The survival analysis used the Kaplan–Meier method[23].

3. RESULTS

3.1 Patients and Treatments

As shown in Figure 1, 56 patients had a wild-type *KRAS* gene, and 44 received at least 1 infusion of panitumumab with or without irinotecan. Of the 44 patients, 7 were treated with panitumumab and irinotecan (physician's choice in clinical practice), and 37, with panitumumab alone.

In the group receiving panitumumab alone, median age was 60 years (range: 41–82 years). Performance status [Eastern Cooperative Oncology Group (ECOG)] varied: 24% were scored 0; 54%, 1; 16%, 2; and 3%, 3 (Table I). All patients had received at least 2 prior lines of chemotherapy; 51.4% ($n = 19$) had received 3 prior lines of chemotherapy, and 8.1% ($n = 3$) had received 4 prior lines of chemotherapy (Table I).

Table II shows the exposure of these patients to panitumumab treatment: 40.5% ($n = 15$) had less than 3 months' exposure (1–5 infusions); 32.4% ($n = 12$) had 3–6 months' exposure (6–12 infusions); 21.6%

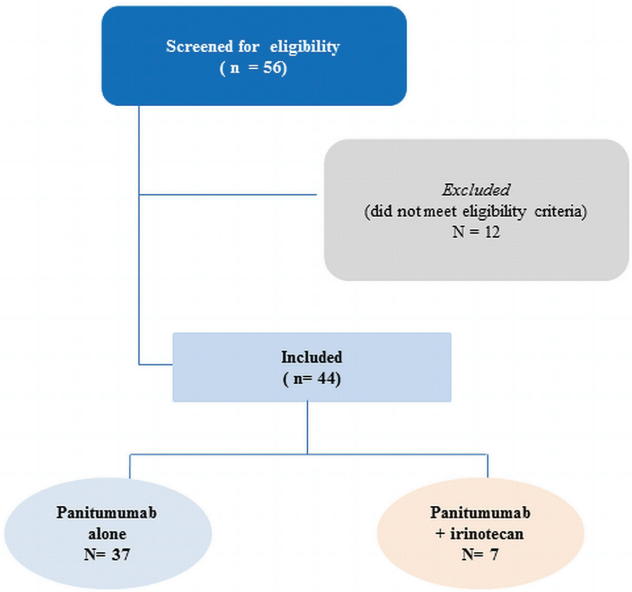

FIGURE 1 CONSORT *diagram for the study.*

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TABLE I Baseline characteristics of patients receiving panitumumab

Characteristic	*Value*
Patients (*n*)	37
Age (years)[a]	
Mean	60±10.6
Range	42–81
Age ≥65 years (*n*)	12
ECOG performance status [*n* (%)]	
0	9 (24.3)
1	20 (54)
2	6 (16.2)
3	1 (2.7)
Prior lines of chemotherapy [*n* (%)]	
1[b]	37 (100)
2[c]	37 (100)
3[d]	19 (51.4)
4[e]	3 (8.1)

[a] At treatment start.
[b] FOLFOX or FOLFIRI ± bevacizumab; capecitabine ± oxaliplatin; 5-fluorouracil–leucovorin.
[c] FOLFOX or FOLFIRI ± bevacizumab; irinotecan; capecitabine.
[d] Oxaliplatin; IROX (irinotecan–oxaliplatin); FOLFIRI; irinotecan.
[e] FOLFOX.
ECOG = Eastern Cooperative Oncology Group.

TABLE II Treatment exposure to panitumumab alone

Exposure	*Value [n (%)]*
Patients	37
Infusions	
1	2
2+	2
3+	4
4	2
5	5
6+	3
7	1
8	2
9+	2
11	1
12+	3
14	2
16	1
18	1
19	1
20	1
21	1
23+	1
29+	2
Treatment exposure	
<3 Months (1–5 infusions)	15 (40.5)
3 to 6 Months (6–12 infusions)	12 (32.4)
>6 to 11.5 Months (14–23 infusions)	8 (21.6)
14.5 Months (29 infusions)	2 (5.4)
Median cycles (*n*)	5

(*n* = 8) had 6–11.5 months' exposure (14–23 infusions), and 5.4% (*n* = 2) had more than 14.5 months' exposure (29 infusions). The median number of infusions was 5. Treatment was discontinued upon disease progression. No patient experienced an adverse event severe enough to require treatment discontinuation.

3.2 Efficacy

We conducted two subanalyses. The first included all 44 patients treated with panitumumab with or without irinotecan. The second included the 37 patients treated with panitumumab alone.

3.2.1 PFS

In the overall group (44 patients), 35 progressions (79.55%) and 9 censored observations (20.45%) were recorded. Median PFS was 20 weeks, with a standard error of 5.8 weeks (95% CI: 13 to 34 weeks). Mean PFS was 28.48 weeks, with a standard error of 4.11 weeks (95% CI: 20.44 to 36.53 weeks). The estimated progression rate of the population was 0.034 new progressions per week (95% CI: 0.024 to 0.047 new progressions per week). Figure 2(A) shows the associated Kaplan–Meyer PFS curve.

In the group receiving panitumumab alone (37 patients), 28 progressions (75.68%) and 9 censored observations (24.32%) were registered. Median PFS was 21.86 weeks (Amado *et al.* reported a median PFS of 12.3 weeks for panitumumab), with a standard error of 5.23 weeks (95% CI: 12.86 to 36.86 weeks). Mean PFS was 27.34 weeks, with a standard error of 3.82 weeks (95% CI: 19.85 to 34.82 weeks). The estimated progression rate of this group was 0.0340 new progressions per week (95% CI: 0.0234 to 0.0492 new progressions per week). Figure 2(B) shows the associated Kaplan–Meier PFS curve.

The addition of irinotecan did not seem to improve PFS [Figure 2(A)].

3.2.2 OS

In the overall group (44 patients), 24 deaths (54.55%) and 20 censored observations (45.45%) were reported. Median OS was 35.14 weeks, with a standard error of 9.24 weeks (95% CI: 24 to 68.57 weeks). The restricted mean OS was 50.36 weeks, with a standard error of 6.50 weeks (95% CI: 37.62 to 63.11 weeks). The restricted mean OS is censored because of the analysis time, but the extended mean OS can be estimated up to 64.09 weeks. The death rate for the population was

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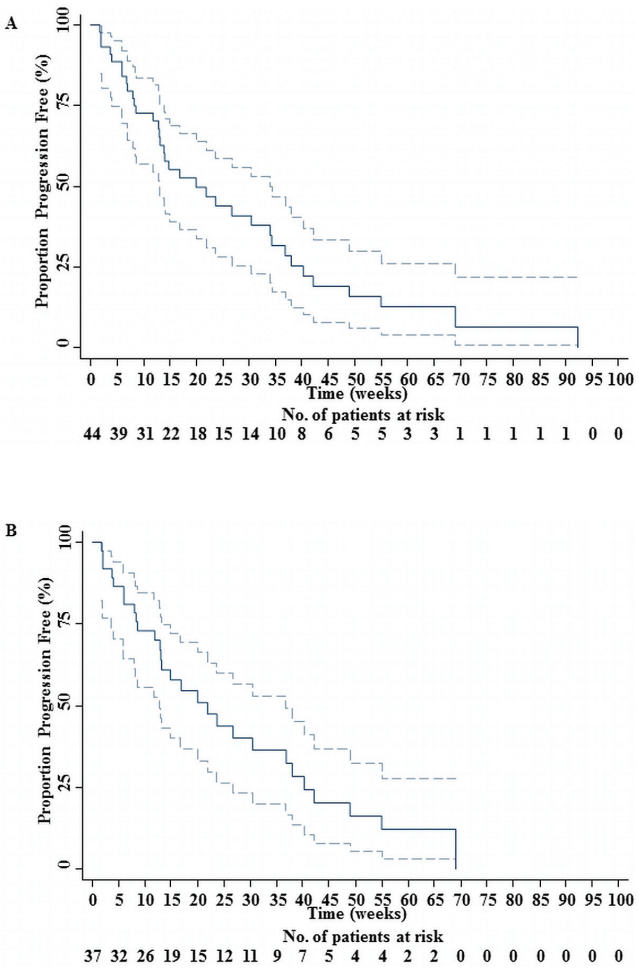

FIGURE 2 (A) Progression-free survival (PFS) for 44 patients receiving irinotecan or panitumumab, or both. The solid line represents the PFS curve for patients treated at the Jewish General Hospital. (B) The PFS for 37 patients receiving panitumumab alone. The solid line represents the PFS curve for patients treated at the Jewish General Hospital. The dotted lines mark the 95% confidence limits.

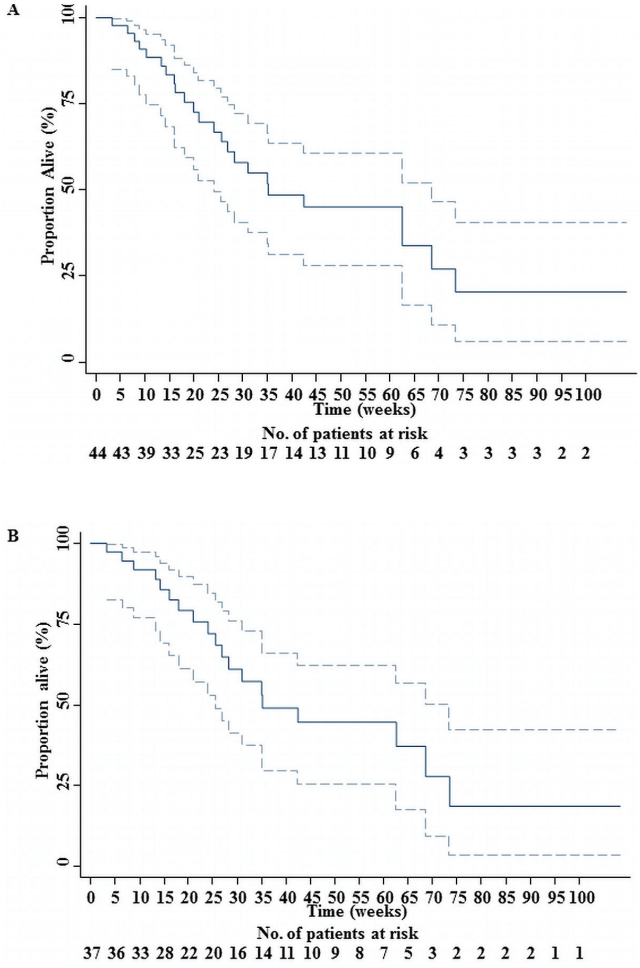

FIGURE 3 (A) Overall survival (OS) for 44 patients receiving panitumumab with or without irinotecan. The solid line represents the OS curve of patients treated at the Jewish General Hospital (B) Overall survival (OS) for 37 patients receiving panitumumab alone. The solid line represents the OS curve of patients treated at the Jewish General Hospital. The dotted lines mark the 95% confidence limits.

estimated at 0.0158 deaths per week (95% CI: 0.0106 to 0.0236 deaths per week). Figure 3(A) shows the associated Kaplan–Meier survival curve.

In the group receiving panitumumab alone (37 patients), 19 deaths (51.35%) and 18 censored observations (48.65%) were recorded. Median OS was 35.14 weeks (Amado *et al.* reported a median OS of 8.1 months for panitumumab), with a standard error of 7.75 weeks (95% CI: 25.57 to 73.43 weeks). The restricted mean was 50.96 weeks, with a standard error of 7.12 weeks (95% CI: 37.00 to 64.91 weeks). Once again, the extended mean OS can be estimated as 62.91 weeks. The estimated death rate of this group was 0.0152 deaths per week (95% CI: 0.0097 to 0.0239 deaths per week). Figure 3(B) shows the associated Kaplan–Meier survival curve.

3.2.3 Safety

Table III lists 11 adverse events investigated in the 37 patients treated with panitumumab alone (clinicians are more likely to associate these symptoms with disease progression, pain, and opiates). The most frequently noted adverse events were skin toxicities (n = 21, 57%) and hypomagnesemia (n = 15, 41%). Grade 3 skin toxicities and hypomagnesemia occurred in 6 patients (16%) and 4 patients (11%) respectively. A grade 3 paronychia was registered in 1 patient (2.7%).

The deaths that occurred among the patients in the panitumumab-only group (n = 20, 54%) were all deemed to be a result of disease progression and not of treatment. Disease progression was determined by clinical deterioration (for example, disabling fatigue) in 12 patients treated with panitumumab alone (32%)

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TABLE III Safety profile related to panitumumab treatment

Adverse event	*Patients experiencing [*n *of 37 (%)]*	
	Any grade	*Grade 3*
Skin or integument toxicity	21 (56.8)	6 (16.2)
Eye toxicity	1 (2.7)	0 (0)
Paronychia	2 (5.4)	1 (2.7)
Abdominal pain	2 (5.4)	0 (0)
Constipation	2 (5.4)	0 (0)
Diarrhea	3 (8.1)	0 (0)
Vomiting	1 (2.7)	0 (0)
Fatigue and general deterioration	12 (32.4)	12 (32.4)
Hypomagnesemia	15 (40.5)	4 (10.8)

and by the once-every-3-months radiologic assessment in 25 patients (68%).

4. DISCUSSION

In this retrospective study, we collected and analyzed the clinical outcomes of treatment with panitumumab in patients with wild-type *KRAS* and progressive mCRC, in whom at least two lines of chemotherapy failed. In the initial study demonstrating the requirement of wild-type *KRAS* for panitumumab efficacy in third-line treatment for mCRC[22], the median age of the patients was 62.5 years, and most patients had a performance status score between 0 (53%) and 1 (56%). Although the age range in our patients was similar, performance status showed more variability, with ECOG scores spanning the entire 0–3 range (most patients had an ECOG score between 1 and 2), likely because our data were collected in a real-world clinical setting rather than in a clinical trial. Our patients had received at least two previous lines of treatment, and in 59.5% of them, panitumumab was used as the fourth or fifth line.

Taken together, the foregoing observations suggest that our patients were performing more poorly than those randomized in the clinical trial conducted by Amado and colleagues[22]. Perhaps as a consequence, our patients received a median of 5 panitumumab infusions compared with the median of 8 infusions in the Amado *et al.* trial. Despite a lower number of infusions for our population, our patients achieved a PFS of 21.86 ± 5.23 weeks (95% CI: 12.9 to 36.9 weeks), which is encouraging compared with the published median PFS of 12.3 weeks in the 2008 study[22]. However, that difference in PFS might also be a result of differences in the assessment of disease progression in clinical practice (imaging frequency or confirmation, clinician assessment) compared with that in a clinical trial setting. Indeed, the OS that we observed was similar to the OS in the registration trial (8.78 months vs. 8.1 months)[7], which is consistent with the idea that PFS is not the best predictor of OS in the heavily pretreated mCRC setting.

We therefore conclude that median PFS with panitumumab treatment looks favourable compared with the PFS documented in a previous report[22]. We observed no differences in OS or safety despite the small size of our population. Also, there appeared to be no differences in efficacy between panitumumab alone and panitumumab plus irinotecan. That observation suggests that panitumumab alone may be the most reasonable choice in this setting, although the small sample size warrants caution in the interpretation.

Interestingly, a French group presented data about the use of panitumumab as a single agent in 269 mCRC patients in real-world practice[24]. Median OS was 6.71 months, which is shorter than that previously described (Amado *et al.*: 8.1 months). The authors attribute the difference to the status of the study as a real-world report and not as a clinical trial enrolling younger patients with better health states.

The most frequently reported toxicities related to panitumumab treatment were skin toxicity and hypomagnesemia. Only grade 3 skin toxicity and hypomagnesemia were reported for both the present study and other published studies[7,22]. Given the small sample size, we could not obtain convincing survival data stratified by the presence or absence of skin reaction, or a lower compared with a normal serum magnesium. Higher grade 3 hypomagnesemia was noted in our setting, probably because our population was heavily pre-treated compared with the patients in the clinical trials. Moreover, the other 9 reported adverse events (eye toxicity, paronychia, anorexia, abdominal pain, constipation, diarrhea, vomiting, fatigue, and general physical deterioration) were less frequent in our study than in other reported studies involving panitumumab treatment[7,22]. No infusion reactions were reported in our setting.

5. CONCLUSIONS

We found that the PFS and OS attained with panitumumab therapy in our setting—heavily pre-treated mCRC patients (>50% with 3+ lines, 8% with 4+ lines) with poorer performance status than is typically permitted in clinical trials—were in line with previously published reports[7,22].

Because real-world data are often required by regional authorities to approve and reimburse medication, we believe that our results are encouraging and that our data may facilitate access by patients to this oncology medication in a real-world setting. Nevertheless, analysis of a larger sample of patients with mCRC is warranted to assess the proper per label use in regular clinical practice.

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6. CONFLICT OF INTEREST DISCLOSURES

All authors declare no financial conflicts of interest.

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