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Single agent panitumumab in KRAS wild-type metastatic colorectal cancer patients following cetuximab-based regimens

Clinical outcome and biomarkers of efficacy

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Background: Few data are available outlining outcomes of panitumumab in advanced colorectal cancer patients benefiting from prior cetuximab-based regimens.

Patients and methods: Thirty patients with KRAS wild type metastatic colorectal cancer with clinical benefit from prior cetuximab-based regimens between May 2004 and October 2011 were reviewed at nine Italian Institutions. Inclusion key criteria included interruption of cetuximab for reasons other than progressive disease. Patients were classified according to prior regimens (0 or ≥1), prior response or stabilization, surgery of metastases, and Köhne prognostic score. At the time of subsequent progression, patients were treated with single agent panitumumab until progressive disease, unacceptable toxicity, or consent withdrawal.

Results: Panitumumab obtained 67% disease control rate and 30% objective response rate, with median PFS of 4.2 and median OS of 9.6 mo. Patients with BRAF/NRAS/PI3KCA and KRAS (by mutant enriched technique) wild-type tumors had the best chance of response to panitumumab.

Conclusions: Single agent panitumumab provided significant clinical benefit in heavily pretreated patients without acquired resistance to prior cetuximab-based regimens.

Introduction

Epidermal growth factor receptor (EGFR) inhibition is routinely used in the treatment of advanced colorectal cancer (CRC). The chimeric monoclonal antibody (moAb) cetuximab (Cmab) and the fully human moAb panitumumab (Pmab) are the commonly used anti-EGFR therapies. Both drugs are indicated as monotherapy in patients with wild-type *KRAS* tumors who are refractory to or have progressed following initial chemotherapy and are also recommended in combination with chemotherapy.[1-6] Of note, it has been well reported that molecular factors including not only *KRAS* mutations, but also *BRAF*, *NRAS*, and *PI3KA* mutations, are predictive of resistance to EGFR therapeutic blockade.[7-11] However, despite initial responses to Cmab-based regimens (CBR) in patients with *KRAS* wild-type advanced CRC, the majority of those patients eventually develop progression. This subsequent failure may be related to mechanisms of acquired resistance such as a drug-mediated selection of tumoral cells harboring *KRAS* mutations,[12] or an anti-chimeric antibody reaction neutralizing Cmab,[13,14] or the EGFR ectodomain acquired mutation (S492R) that prevents the binding with Cmab, but not with Pmab.[15]

Currently, the efficacy of single agent Pmab as rechallenge is under evaluation by few studies. However, the results were based on the population with heterogeneous clinical characteristics and no control group has been included in the published studies, with inconsistent results focused on the clinical activity of Pmab administration after CBR failure. Indeed, a previous retrospective or non-randomized study suggested that Pmab treatment after failure on prior Cmab could have a minimal benefit.[16] By contrast, no objective response and short progression free survival and overall survival was reported by Wadlow et al.[17] Therefore, the efficacy of "rechallenge" with Pmab following Cmab failure remains unclear.

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Here, the outcomes of single agent Pmab in *KRAS* wild-type metastatic CRC patients without progression on prior CBR and the potential role of biomarkers for patients selection were investigated through a multicenter, cooperative, observational prospective study.

Results

Patients characteristics

A total of 30 patients with *KRAS* wild type advanced CRC were collected. At the time of start of CBR, patients demographic, and baseline clinical characteristics as shown in **Table 1**. Patients' ages ranged from 44 to 81 y (median, 67 y) and 73% of the patients were male. Patients were classified according to Köhne prognostic score as low (14/30, 47%), intermediate (12/30, 40%), or high risk (4/30, 13%)

According to the RECIST criteria, all patients had measurable lesions and were evaluable for response. CBR were given as the first line treatment in 6 (20%) patients, second line in 10 (33%), third or more line in 14 (47%). Causes of CBRs discontinuation were: scheduled treatment completion after at least a 6-mo treatment period (16/30, 53%), surgery of metastases (4/30, 13.5%), patient's choice (4/30, 13.5%), and adverse events (AE) (6/30, 20%). At the time of start of Pmab, patients' demographic and baseline clinical characteristics are shown in **Table 2**. Pmab was the second line treatment in 3 (10%) patients, third line in 8 (27%), fourth or more line in 19 (63%). Median interval between CBR and Pmab treatment was 13 mo (ranged from 8 to 39 mo). The performance status was mainly ECOG 0 (12/30, 40%) or 1 (16/30, 53%), while only 2 (7%) patients had poor ECOG PS score of 2; median age was 68 y (range, 44–83) and almost all patients (90%) had received more than two systemic therapy regimens before Pmab. Chemotherapy was administered between last CBR and subsequent Pmab in 9 of 30 patients (30%). Two patients were still on treatment without signs of PD at the time of this analysis; among progressing patients, 20/28, (71%) subsequently did not receive further treatment due to ECOG performance status rapid deterioration. Eight patients underwent chemotherapy rechallenge, with 2 PR and 4 SD (all lasting <6 mo) and 2 PD.

Response and survival

During CBR, CR was observed in 1 patient (3%), PR in 17 (57%), and SD in 12 (40%). When treated with Pmab, 9 patients showed PR (30%), 11 patients remained SD (37%), and the remaining 10 showed PD (33%), with a disease control rate (PR + SD) of 67% (**Table 3**). Objective response while on prior CBR, as compared with SD, was associated with a trend for higher response rate for Pmab (7/18, 40% vs. 2/12, 17%; $P = 0.2$). Disease control rate with Pmab was clinically meaningful and was the same (67%) in both groups with PR/CR vs. SD on Cmab.

The median follow-up period for the analysis from the date of CBR start was 23 mo and, by the time of the final analysis on 26 December 2012, 24 (80%) patients had succumbed (6 patients were still alive). At a median follow up of 13.5 mo from the start of Pmab, median PFS, and OS obtained with single agent Pmab were 4.2 and 9.6 mo, respectively. Median PFS calculated from the start of Cmab was 8 mo. On the other hand, median OS calculated from the start of Cmab was surprisingly high and corresponded to 26.9 mo.

Table 1. Baseline characteristics prior to cetuximab-based regimens

Variables		
Age (years)	***n* = 30**	**Percent (%)**
≥70	10	33
<70	20	67
Sex		
Male	22	73
Female	8	27
Line of cetuximab-based regimens		
1st-line	6	20
2nd-line	10	33
≥3rd-line	14	47
ECOG performance status		
0	27	90
1	3	10
Köhne prognostic score		
Low risk	14	47
Intermediate risk	12	40
High risk	4	13

Treatment outcome according to KRAS/NRAS/BRAF/PI3CKA status

Tissue blocks were available for 21 patients treated with single agent Pmab and consenting for biomolecular analyses. Pre-treatment samples were obtained from 14 (67%) primary tumors and 7 (33%) resected metastases. No *NRAS* and *BRAF* mutations were detected. With mutant enriched PCR we identified 3 *KRAS* mutated samples that were diagnosed as wild-type by standard Sanger sequencing (1 G13D, 1 G13S, 1 G12D): all three patients showed a partial response to CBR, but failed to respond to Pmab (2 SD/1 PD). *PI3KCA* activating mutations involving exon 9 (E545K in 1 case) and exon 20 (H1047R in 2 cases) occurred in 3 of 19 (16%) cases (two cases were not evaluable), and were mutually exclusive with *KRAS* mutations. All three patients had clinical benefit on CBR (1 PR/2 long lasting SD) but subsequently had SD as best response (2 SD/1 PD) to Pmab. Thus, all 6 patients with either *PI3KCA* or *KRAS* mutations (detected by mutant enriched technique) failed to respond tosingle agent Pmab, while 6 out of 15 (40%) with *KRAS/BRAF/NRAS/PI3KCA* wild-type responded to anti-EGFR rechallenge ($P = 0.12$ by the Fisher exact test).

Discussion

Although patients without *KRAS* mutations may be highly sensitive to CBR, long-term Cmab administration can result in the development of acquired resistance through several molecular mechanisms.[12] Both Cmab and Pmab have been in routine use in

Table 2. Baseline characteristics prior to single agent panitumumab

Variables	Panitumumab	
	N = 30	Percent (%)
Age (years)		
≥70	10	33
<70	20	67
Prior cetuximab-based regimens		
1st-line	6	20
2nd-line	10	33
≥3rd-line	14	47
Conventional chemotherapy between cetuximab-based regimens and panitumumab		
0	21	70
1	5	17
≥2	4	13
ECOG performance status		
0	12	40
1	16	53
2	2	7
Panitumumab line		
2nd-line	3	10
3rd-line	9	30
≥4th-line	18	60

KRAS wild-type advanced CRC for the recent years,[2-8] but little is known about the efficacy of a salvage Pmab monotherapy after prior CBR.

In the present study, the objective responses and the disease control rate for single agent Pmab in *KRAS* wild-type metastatic colorectal cancer patients without progression on prior CBR were 30% and 67%. A higher response rate on single agent Pmab was associated with objective response to prior CBR (40% vs 17% for patients with prior SD; $P = 0.2$). In addition, the PFS and OS for Pmab treatment were 4.2 and 9.6 mo, respectively. Our findings highlight the clinical utility of anti-EGFR treatment rechallenge if acquired resistance has not occurred clinically. Consistently, although small and retrospective analyses reported the possibility of disease control, including objective responses, with the use of Pmab after CBR failure,[14] recently, it was shown that Pmab rechallenge has minimal benefit in patients with *KRAS* wild-type colorectal cancer with disease progression during Cmab.[16] In particular, no objective response was recorded, observing PFS and OS of 1.7 and 5.2 mo, respectively. Considering the similar mechanism of these two anti-EGFR moAb, it seems unreasonable to administer a rechallenge with the same class drug in patients with acquired resistance. The logical treatment approach for these patients is to combine anti-EGFR treatment with drugs which can overcome the resistance mechanism. Currently, several novel agents including second-generation anti-EGFR moAb or agents targeting the hepatocyte growth factor receptor, c-Met, are being developed for the treatment of advanced CRC.

Moreover, the phase II PANERB trial prospectively treated 32 *KRAS* wild-type advanced CRC patients with Pmab after failure of irinotecan plus Cmab regimens. Remarkably, in line with our data, it was reported that higher responses (22%) and disease control (73%) rates were associated with single agent Pmab when considering only the 11 patients who had previously responded to cetuximab and irinotecan.[18] Some reports have suggested that CBR failure is possibly related to an anti-chimeric antibody reaction neutralizing Cmab or acquired mutations of the EGFR extracellular domain that may predict resistance to Cmab, but not Pmab.[13-15] This may allow an activity of single agent Pmab treatment after CBR failure in patients who have no KRAS mutations and exhibit initial disease control while on Cmab.

Another possibility is the loss of acquired-resistance after an anti-EGFR free interval. Conventional chemotherapy given after CBR failure may also result in reduction of anti-EGFR resistant clones, leaving the sensitive ones to be further controlled by a subsequent rechallenge. Recently, a phase II, prospective study focused on the role of Cmab- plus irinotecan-based therapy rechallenge in 39 advanced *KRAS* wild type colorectal cancer.[19] Eligibility criteria included initial benefit from Cmab and subsequent acquired resistance, followed by interval chemotherapy and, at the time of PD, Cmab rechallenge. This strategy led to highly promising response rate of 53.8% and median PFS of 6.6 mo after Cmab rechallenge. Nine of the 30 patients in our series received conventional chemotherapy during anti-EGFR therapy-free intervals. However, an association between disease

Table 3. Response to cetuximab-based regimens and to single agent panitumumab ($N = 30$).

Response	Cetuximab-based regimens		Single agent panitumumab	
	No	%	No	%
Complete response (CR)	1	3	0	0
Partial response (PR)	17	57	9	30
Stable disease (SD)	12	40	11	37
Progressive disease (PD)	0	0	10	33
Disease control rate (CR + PR + SD)		100	20	67

control with chemotherapy and the second anti-EGFR in this small group of patients is not demonstrable. Above all, the direct comparison between rescue Pmab vs. Cmab is not possible at present, since a randomized prospective trial would be required. However, our strategy is particularly valuable due to: (1) the easy way of administration of Pmab as single agent, biweekly, and chemotherapy-free treatment; thus, the possibility to administer Pmab—in place of irinotecan plus Cmab—to patients with poor performance status, (2) the eventual occurrence of prior allergic reactions to the chimeric portion of Cmab, (3) the non-complete cross resistance mechanisms between the two anti-EGFR MoAb, and (4) regulatory agencies limitations in the rechallenge with the same drug after all-causes discontinuation.

The correlation between the status of specific biomarkers and the disease outcome of patients treated with anti-EGFR treatment rechallenge has never been considered in previous studies. Here, even if number of samples was restricted (21 cases), we performed the mutational analysis of *KRAS, BRAF, NRAS*, and *PI3KCA*. Interestingly, the 6 patients with a tumor sample harboring *KRAS* or *PI3KCA* mutations failed to respond to Pmab, while 6 out of 15 with wild-type *KRAS/BRAF/NRAS/PI3KCA* responded. Of note, *KRAS* mutations were here assessed using the mutant enriched PCR assay, a methods more sensitive than Sanger sequencing.[20] It is exciting to speculate that, due to tumor heterogeneity, low prevalent *KRAS* mutant clones identified through high sensibility techniques in the samples collected prior to CBR, may have subsequently emerged during single agent Pmab and have been responsible of acquired resistance. *KRAS* mutations were located in codon 13 in 2 of 3 cases—possibly indicating a non-complete resistance mechanism which was previously hypothesized for cetuximab, but not for panitumumab. This may explain the response to prior CBR and the absence of benefit from Pmab in our patients harboring *KRAS* codon 13 mutations.[21,22] Moreover, the lack of BRAF mutant tumors may derive from the poor prognosis associated with this biological feature[23] and lead to rapid performance status deterioration prior to patients selection for anti-EGFR rechallenge.

Due to the lack of a control group, it cannot be ruled out that the observed benefit of single agent Pmab in previous studies[16-18] was attributed to the confounding effects. In view of the absence of randomized assignments, our study shows similar potential bias and it is controversial whether the survival benefit was related to Pmab or to patient selection. Indeed, the patients included in the present study represent a prospectively-collected, multi-institutional database of consecutive patients, characterized by heavy exposure to systemic therapies, performance status as much good as to allow further anticancer treatment and high sensitivity to anti-EGFR treatments.

We found evidence for clinical benefit with single agent Pmab in *KRAS* wild-type metastatic colorectal cancer patients without progression on prior CBR, with satisfactory outcome in a significant proportion of heavily pretreated subjects who were considered still potentially sensitive to EGFR inhibition. The role of administering a second anti-EGFR moAb after failure of the first drug in KRAS wild-type advanced CRC warrants further prospective confirmation. Moreover, further understanding of resistance mechanisms in each individual patient may represent a key to optimizing the use and sequence of Cmab and Pmab therapies, along with their possible combination with newer targeted agents to overcome molecular resistance.

Materials and Methods

Patients

From May 2004 to October 2011, 30 patients with pathologically diagnosed *KRAS* wild-type advanced CRC received CBR at 9 Italian Institutions. A retrospective review of medical and radiographic records was undertaken. The inclusion key criteria were defined as absence of progressive disease (PD) while on prior CBR and subsequent treatment with Pmab at the dosage of 6 mg/kg every two weeks at the time of disease progression. We included patients who received the second anti-EGFR immediately after stopping the first anti-EGFR, as well as those who received the second anti-EGFR any length of time later, with or without conventional chemotherapy being administered between the two treatments. Each patient was stratified according to the following clinical variables: number of regimens administered prior to CBR (0 or ≥1), tumor response to CBR, i.e., partial response (PR)/complete response (CR) or stable disease (SD), Köhne prognostic score,[24] and posttreatment surgery of metastatic sites. All living patients were followed up until December 2012.

Treatment and response evaluation

Treatment response was evaluated according to the Response Evaluation Criteria in Solid Tumors (RECIST) criteria.[25] Response assessment was from review of patient records and radiographic studies including computed tomographic scans, which were performed according to institutional guidelines. Disease control was defined as radiographic evidence of

improvement or stability (PR/CR or SD), associated with clinical alleviation or stability of symptoms as assessed by the treating physician, and continuation of drug treatment. Progression was defined as a radiographic worsening of existing lesions or the appearance of new lesions.

KRAS/NRAS/BRAF/PI3CKA mutation analysis

Formalin-fixed paraffin-embedded tumor tissues were reviewed for quality and tumor content. A tissue containing at least 80% of neoplastic cells was selected for each case. Microscopic dissection of 7 μm methylene blue-stained sections allowed the separation of neoplastic and normal cells. Genomic DNA was extracted using the Qiamp FFPE DNA kit (Qiagen) following manufacturer's instructions. Mutational analysis of *KRAS* exon 2 and 3 was performed as previously described.[11] *KRAS* exon 2 status was further confirmed through a specific mutant enriched PCR, known to be a more sensitive approach.[20] *BRAF* (exons 15), *NRAS* (exon 2), *PI3KCA* (exons 9 and 20) mutational analysis was performed by means of PCR using specific primers previously described.[11,26] The PCR products were subjected to direct sequencing using 3500 DX Genetic Analyzer (Applied Biosystems) and then evaluated by means of the ChromasPro software.

Statistical analysis

The primary endpoint of our study was response rate of single agent Pmab. Secondary endpoints included: disease control rate, which was defined as the sum of patients with both PR/CR and SD; progression-free survival (PFS), which was measured from the first day of Pmab treatment until the first objective or clinical sign of disease progression or death.; overall survival (OS) was defined as the period from the start of Pmab until the date of death or last follow-up.

Disclosure of Potential Conflicts of Interest

No potential conflict of interest was disclosed.

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