Health-related quality of life in patients with RAS wild-type metastatic colorectal cancer treated with panitumumab-based first-line treatment strategy: A pre-specified secondary analysis of the Valentino study

Health-related Quality of Life in *RAS* wild-type metastatic colorectal cancer patients treated with panitumumab plus FOLFOX induction followed by single-agent panitumumab or panitumumab plus 5-FU/LV maintenance: the secondary endpoint of the *Valentino* study

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Abstract

Background

Patient-reported outcomes (PROs) are crucial to estimate the impact of cancer treatments on Quality of Life (QoL), but data from pivotal first-line trials in metastatic colorectal cancer (mCRC) are scanty. The *Valentino* study showed that de-escalation to single-agent panitumumab after a 4-month induction with panitumumab plus FOLFOX (Arm B) is inferior, in terms of progression-free survival (PFS) to panitumumab plus 5-FU/LV (Arm A) in *RAS* wild type mCRC patients, though slightly reducing toxicity. Here we report QoL, a secondary study endpoint.

Methods

PROs were assessed by EORTC QLQ-C30, EORTC QLQ-CR29, EuroQol EQ-5D questionnaires, at baseline and every 8 weeks until disease progression. First two evaluations correspond to induction treatment (identical in both arms), while subsequent evaluations were during maintenance. In order to describe changes in QoL over time, mean changes from baseline at each timepoint were calculated in the overall study population. In order to compare maintenance phase between the two study arms, mean changes versus baseline and proportion of improved/stable/worse patients versus baseline were compared for each QoL item.

Results

In Arm A/B, 91.5%/92.0% of enrolled patients completed the questionnaires at baseline; compliance reduced progressively at the following timepoints, without significant differences between the two arms. No significant differences in the two arms were reported both in baseline scores and in mean changes versus baseline for the three questionnaires during the maintenance phase (at 24, 32, 40 weeks). In the overall population, mean changes versus baseline showed an early deterioration during induction but a partial recovering in the maintenance phase for global QoL, functional scales and several symptoms (fatigue, nausea/vomiting, appetite loss, diarrhea) of QLQ-C30, a number of symptoms/items related to social functioning (body image, dry mouth, hair loss, taste, faecal incontinence, sore skin) of QLQ-CR29, and VAS score of EQ-5D.

Conclusions

In *RAS* wild-type mCRC patients, induction treatment with oxaliplatin-containing chemotherapy plus anti-EGFRs induces a transient significant QoL deterioration. After an induction phase, treatment de-intensification determines an overall recovery of health-related QoL, besides the expected prevention of oxaliplatin-related neurotoxicity.

Keywords

Quality of life; colorectal cancer; metastasis; chemotherapy; maintenance treatment; EGFR inhibitor

Introduction

The therapeutic outcome of patients with metastatic colorectal cancer (mCRC) has been significantly improved in recent years, thanks to the introduction of biological agents combined with chemotherapy regimens, as well as to the integration of systemic treatments with potentially curative surgery[1,2].

Nevertheless, the optimal treatment choice in cancer patients should take into account also the tolerability and the impact on patients' quality of life (QoL) of the available therapeutic options[3]. In mCRC, highly active intensified regimens such as FOLFOXIRI triplet chemotherapy plus bevacizumab or anti-EGFR-based doublet combinations, which are used as the most effective first-line options and in cases in which a conversion-to-surgery with radical approach is planned, are associated with a significant toxicity burden[4-6]. On the other hand, with the aim to reduce the cumulative toxicity of prolonged first-line treatment, several randomized clinical trials have investigated de-escalation strategies after an induction phase, such as fluoropyrimidine-based maintenance treatments, showing an improvement in the safety of therapies without jeopardizing the efficacy outcomes[7-10].

In this scenario, patient-reported outcomes (PROs) are crucial in order to estimate the real impact of anti-neoplastic treatments on the QoL of cancer patients and to help clinicians to adjust the therapeutic algorithm, balancing the benefits and risks of oncologic treatments[11,12]. Whilst relevant evidence on this topic has been collected in other tumor settings, for what concerns mCRC, few data have been obtained from the pivotal first-line trials including doublet or triplet chemotherapy regimens plus or minus biologic agents[13]. In fact, most trials did not include PROs in the primary or secondary study endpoints, and in other cases, results on QoL analyses have not been released yet; moreover, in the few trials reporting on QoL, the questionnaires and the analytical methodology were heterogeneous[14]. Therefore, the true impact of the intensification and de-escalation of treatment regimens on the QoL of patients with mCRC is still far to be elucidated, and, on the other hand, the optimal tools and measures to evaluate PROs in this setting have to be clearly established.

The *Valentino* randomized phase II trial showed that de-escalation to single-agent panitumumab after a 4-month induction with panitumumab plus FOLFOX is inferior, in terms of progression-free survival (PFS), to panitumumab plus 5-FU/LV maintenance in *RAS* wild type mCRC patients, although slightly reducing the toxicity burden[10]. In the *Valentino* study, the analysis of QoL assessed through PROs was a pre-specified secondary endpoint. Randomization was performed before the start of induction treatment, and this allows the

description of changes in QoL during both induction and maintenance phase, in the whole study population and in the two treatment arms separately.
Here we report the results of the QoL analysis of the study.

Materials and Methods

Study design and trial population

The *Valentino* study (*NCT02476045*) was a multicenter, randomized, open-label phase II trial designed to evaluate the non-inferiority in terms of PFS of maintenance with single-agent panitumumab (Arm B) versus panitumumab plus 5-FU/LV (arm A) after an induction treatment with panitumumab plus FOLFOX-4 in *RAS* wild-type mCRC patients[10]. The trial enrolled 229 patients (117 and 112 in Arm A and B, respectively). Main inclusion criteria were: histologically confirmed CRC with *RAS* wild-type status confirmed by approved methods, ECOG performance status 0-1, no previous treatment for metastatic disease, unresectable metastases, measurable or evaluable disease according to RECIST v1.1, availability of baseline tumor samples to be centrally collected at the Coordinating Center (Fondazione IRCCS Istituto Nazionale dei Tumori). Patients were excluded if they had relapsed during adjuvant oxaliplatin-based chemotherapy or within 12 months from its completion (or within 6 months for adjuvant fluoropyrimidine monotherapy) or in case of significant comorbidities.

Quality of life analysis

PROs were assessed by European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire – Core 30 (QLQ-C30)[15], and the colorectal cancer specific module (EORTC QLQ-CR29)[16], EuroQol – 5D (EQ-5D)[17] questionnaires.
EORTC QLQ-C30[15] is a 30-item questionnaire composed of five multi-item functional subscales (physical, role, emotional, social, and cognitive functioning), three multi-item symptom scales (fatigue, pain and emesis), a global health status subscale, and six single items to assess financial impact, dyspnea, sleep disturbance, appetite, diarrhea, and constipation, during the previous week. Global QoL is measured by items 29 (“How would you rate your overall health during the past week?”) and 30 (“How would you rate your overall quality of life during the past week?”). With the exception of items 29 and 30, that have seven response categories, all the remaining items have the same four response categories: "Not at all", "A little", "Quite a bit" and "Very Much". According to EORTC QLQ-C30 scoring manual, scores for

multi-item scales are calculated by deriving mean raw scores of single items and transforming them linearly into scales ranging from 0 to 100[18]. For single items, only linear transformation is performed.

EORTC QLQ-CR29 contains 29 items[16]. There are 18 items addressing gastrointestinal symptoms, pain and problems with micturition, and there are separate scales for the participants with or without a stoma and separate items addressing sexual function for men and women. All the items have the same four response categories as EORTC QLQ-C30. Calculation of scores for multi-item scales (urinary frequency, blood and mucus in stool, stool frequency and body image) and linear transformation for single items is performed similarly to QLQ-C30.

The EQ5D-VAS[17] records the respondent's self-rated health on a vertical, 20-cm visual analog scale, in which the end points are labeled “best imaginable health state” and “worst imaginable health state.” This answer can be used as a quantitative measure of health outcome as judged by the respondent.

PROs were administered at baseline and every 8 weeks until disease progression. The first two reassessments (after 8 and 16 weeks) correspond to induction treatment (identical in both arms), while subsequent evaluations (from 24 weeks on) correspond to the randomly assigned maintenance strategy differing between the 2 arms.

According to the National Cancer Institute of Canada Clinical Trials Group QoL framework[11], missing QoL data were reported under different scenarios: (1) rate of patients completing baseline assessments and the assessments at designated time points over the total number of randomized patients; (2) rate of patients completing assessments at designated time points while on study over the total number completing assessment at baseline; and (3) rate of patients completing assessments at designated time points over the number of patients still on study, who were expected to complete questionnaires at each of those time points (excluding those who progressed or were dead at that time point).

For each domain or symptom of EORTC QLQ-C30 and QLQ-CR29, mean changes from baseline to each of the planned time points were reported. A positive value represents an improvement for global health status and functional scales, and a worsening for symptom scales. For comparison between treatment arms at each time point, differences from baseline

scores were compared by a multivariable linear regression model, using baseline values as covariates. The first 2 assessments (after 8 and 16 weeks) were not formally compared because induction treatment was in principle the same in both arms, and differences could be attributed to chance. Subsequent time-points (24, 32, 40 weeks, and treatment discontinuation due to progressive disease) were formally compared. In the whole study population, comparison of each time point vs. baseline was performed by T test for paired data.

In addition to mean changes from baseline, for each domain of EORTC QLQ C30, QoL response from baseline was derived for each domain or symptom as follows: a change score of at least 10 points from baseline was defined as clinically relevant, as suggested by Osoba et al[19]. Patients were considered improved if they reported a score of 10 points or more better than baseline at any of the first three questionnaires after maintenance start (24 weeks, 32 weeks, and 40 weeks), and were considered worsened if they reported a score 10 or more points worse than baseline (without improvement). The remaining patients, whose scores changed less than 10 points from baseline, were considered stable. Best QoL response was compared between treatment arms by chi square test. In the whole study population, QoL response was described separately at each of the first 5 assessments, including both induction and maintenance phase (8, 16, 24, 32 and 40 weeks).

For comparison of EQ-5D VAS between treatment arms at each time point, differences from baseline scores were compared by a multivariable linear regression model, using baseline values as covariates. In the whole study population, comparison of EQ-5D VAS at each time point vs. baseline was performed by T test for paired data.

Because of the exploratory nature of the QoL analysis, adjustment for multiple item comparisons was not performed and $p < 0.05$ was considered statistically significant.

Results

Compliance analysis

Out of the 229 patients enrolled and randomized in the trial, a total number of 210 patients completed the QLQ-C30, QLQ-CR29 and EQ-5D questionnaires at baseline and were considered for the PROs analyses, 107/117 in Arm A and 103/112 in Arm B. Therefore, the compliance at baseline was 91.5% and 92.0% in Arm A and B, respectively. The rate of

patients completing the assessments at designated time points over the total number of randomized patients and the rate of patients completing assessments at designated time points while on study over the total number completing assessment at baseline progressively decreased at the following timepoints (**Figure 1A/B**). The rate of patients completing the three questionnaires at each pre-specified timepoint upon the total number of patients still on study, who were expected to complete the questionnaire, was maintained around or above 80% in the two treatment arms until week 48 (**Figure 1C**). The compliance, reported with the three modalities, was similar between the two arms at any timepoint, as illustrated in **Figure 1**.

Patients and disease characteristics

Overall, in the final PROs dataset, median age was 63.5 (IQR 55.4-69.8) years and baseline Eastern Cooperative Oncology Group Performance Status (ECOG PS) was 0 and 1 in 65.7% and 34.3% of cases, respectively. Overall, patients with 1 and >1 metastatic site accounted for 55.7% and 44.3%, respectively, patients with liver-limited disease were 35.2% and those with peritoneal localizations were 22.9%. The global rate of presence of *BRAF* mutation was 3.8% and of right-sidedness 15.7% (**Table 1**).

QoL analysis in patients stratified in the two treatment arms

QLQ-C30

There were no significant differences between the two arms in baseline scores for global QoL, functional scales and symptoms. In details, in Arm A versus B, mean score (standard deviation) at baseline was 65.19 (18.94) versus 67.48 (21.15) for global QoL. Further details are shown in (**Table 2**).

During the maintenance phase, at the pre-defined timepoints of 24, 32 and 40 weeks, no significant differences were found between the two arms in terms of mean changes versus baseline of global QoL (-2.6/-1.75, p=0.74; -1.55/0, p=0.58; +0.29/0, p=0.80 at 24, 32, 40 weeks in Arm A and B, respectively), functional scales and all the individual symptoms (**Figure 2A**).

Regarding the best response versus baseline analysis, no significant differences between the two treatment arms were reported in the proportion of improved, stable and worse patients considering the best response overall (including the global variation in mean scores in the three timepoints, 24, 32 and 40 weeks) for global QoL (p=0.88), physical (p=0.90), role

(p=0.95), emotional (p=0.09), cognitive (p=0.97) and social functioning (p=0.99), and individual symptoms (**Supplementary Table 1**).

QLQ-C29

In QLQ-CR29, the mean scores at baseline for all the items did not show statistically significant differences between patients in Arm A and B, as illustrated in **Supplementary Table 2.** Consistently, no significant differences were reported in mean changes versus baseline between the two treatment arms, for all the individual items of the questionnaire (**Supplementary Figure 1**).

EQ-5D

Accordingly, for what regards the Visual Analogue Scale (VAS) of the questionnaire EQ-5D, no significant differences between Arm A and B were reported, at 24 (p=0.68), 32 (p=0.28) and 40 (p=0.80) weeks, respectively (**Figure 2B**).

QoL analysis in the overall population

QLQ-C30

In the overall study population, mean changes versus baseline showed a significant early deterioration of global QoL during the induction treatment phase (-4.25, p=0.004 at 8 weeks and -2.84, p=0.11 at 16 weeks), but a progressive recovering in the maintenance phase (-2.27, -0.94, +0.18 at 24, 32, 40 weeks, respectively, although not statistically significant). Similarly, all the five functional scales and several symptoms (specifically fatigue, nausea/vomiting, appetite loss, diarrhea) significantly worsened during induction, with partial recovering during maintenance, as depicted in **Figure 3A**.

The best response versus baseline analysis in the overall population was performed for global QoL and a trend towards an increase in the improved versus stable/worsened categories from the treatment start to week 40th was evidenced, as illustrated in **Figure 4**.

QLQ-C29

Consistently with QLQ-C30, in QLQ-CR29 analysis for mean changes versus baseline, a number of symptoms or items related to social functioning (body image, dry mouth, hair loss, taste, faecal incontinence, sore skin) significantly worsened during induction, and partially recovered during maintenance (**Supplementary Figure 2**).

EQ-5D

The VAS score of EQ-5D showed, in the mean changes versus baseline analysis in the overall trial population, a significant deterioration during the induction phase, with a partial recovering in the maintenance phase (-3.97, p=0.001 at 8 weeks; -4.19, p=0.007 at 16 weeks; -

4.71, p=0.02 at 24 weeks; -3.77, p=0.06 at 32 weeks and -1.45, p=0.62 at 40 weeks), with a further significant deterioration at the time of disease progression (-4.38, p=0.015) (**Figure 3B**).

QoL analysis and primary tumor sidedness

In patients stratified according to primary tumor sidedness, no significant differences were found in terms of mean scores at baseline for global QoL, functional scales and individual symptoms of QLQ-C30 and for all the items of QLQ-CR29. Accordingly, the mean changes versus baseline of global QoL did not significantly differ between patients with left- and right-sided tumors at any of the pre-specified timepoints of both induction and maintenance phase (**Supplementary Figure 3**).

Discussion

In this pre-specified secondary endpoint analysis of the *Valentino* study, we reported the results of health-related QoL assessed through PROs in patients with previously untreated *RAS* wild type mCRC receiving a 4-month induction with panitumumab plus FOLFOX followed by maintenance treatment with either single agent panitumumab or the same induction regimen followed by panitumumab plus 5FU/LV.

In our study, considering the overall trial population, we reported a global deterioration of QoL during the induction treatment, followed by a relevant recovering in the maintenance phase. Specifically, such trends were observed for global QoL, all the five functional scales, and some individual symptoms (fatigue, nausea/vomiting, appetite loss, diarrhea), in QLQ-C30, a number of symptoms or items related to social functioning (body image, dry mouth, hair loss, taste, faecal incontinence, sore skin) in QLQ-CR29 and VAS in EQ-5D. Since our results are internally consistent, they highlight how an intensified treatment regimen may negatively impact the patients' QoL, and reinforce the rationale for de-intensification strategies after an initial induction phase in order to improve QoL, beside decreasing the dose-cumulative adverse events, such as oxaliplatin-related neurotoxicity.

These results are peculiarly relevant in light of the characteristics of this patient population. In details, the patients enrolled in the Valentino trial had *RAS* wild-type tumors, with a negligible proportion of *BRAF* mutations and only 15% rate of right-sided primary tumor location, limited disease burden with single-metastatic site in more than half of them, and good ECOG PS (0 or 1). In fact, in this population with more favorable prognostic outcomes and lower disease burden and disease-related symptoms at baseline, the treatment toxicity may have a crucial impact on QoL in several patients[1].

Pivotal trials in mCRC provided evidence that de-escalation strategies are able to significantly reduce the drug-related toxicity burden, without jeopardizing the survival outcomes[7,20-22]. However, QoL data were not widely reported from trials investigating maintenance strategies, and most of them are derived from bevacizumab-based maintenance trials. In details, in a subgroup of 492 (88%) evaluable patients enrolled the CAIRO3 study, maintenance therapy with metronomic capecitabine plus bevacizumab did not impair patients' QoL assessed by the mean QoL score of QLQ-C30 compared to observation after induction with CAPOX plus bevacizumab[8]. Consistently, in the AIO 0207 trial, in the QoL secondary analysis conducted on nearly the whole study population, maintenance treatment with bevacizumab alone or plus 5-FU/LV was not associated with a detrimental effect on QoL, assessed with QLQ-C30 and QLQ-CR29, compared to observation, and no significant differences were reported between the two maintenance arms[23]. However, since patients enrolled in both trials were randomized after the induction treatment, the impact of induction therapy on patients' QoL could not be evaluated. Moreover, treatment-related toxicities may have a relatively worse impact in patients who do not achieve disease control after the induction phase and may undergo to more rapid PS deterioration, being ineligible for maintenance trials.

On the other hand, for what concerns QoL analysis in first-line pivotal trials including anti-EGFR agents, few data are currently available[24-26]. In details, the addition of cetuximab to FOLFIRI did not significantly impair QoL assessed with QLQ-C30 in the CRYSTAL trial, even if such secondary analysis was conducted in the *KRAS* wild-type subgroup and not in the all-*RAS* wild-type one[27]. A similar result was shown for panitumumab added to FOLFOX-4 in a retrospective analysis of the *RAS* wild-type population of the PRIME study, even if the QoL was evaluated only by means of the EQ-5D questionnaire, that is a less objective and standardizable scale[28]. At present, QoL data from trials investigating maintenance treatment strategies with anti-EGFRs are still lacking[21,22,29,30].

The Valentino study, to our knowledge, is the first randomized clinical trial providing prospective QoL results on a *RAS* wild type mCRC patients' population treated with an anti-EGFR-based first-line strategy. Moreover, in our trial, the compliance to the QoL assessment compared favorably with most trials in the same setting[8,31,32].

We did not observe significant differences between the two maintenance treatment arms for all the outcomes measured in the three questionnaires used (EORTC QLQ-C30, QLQ-CR29 and Euro QoL EQ-5D), regarding both the mean scores at baseline and the mean changes versus baseline at any pre-specified timepoint of the maintenance treatment phase. Additionally, the

proportions of responders versus baseline in QLQ-C30 questionnaire did not significantly differ between the two arms, both at 24 weeks and at the combined analysis including the three analyzed timepoints of the maintenance phase. Therefore, a maintenance strategy combining 5FU/LV mono-chemotherapy with panitumumab did not significantly impair patients' QoL, though slightly increasing the toxicity burden as previously reported[10].

Our study is endowed with a number of limitations. First of all, the study design including randomization before the start of induction, on the one side allowed us to investigate the impact on QoL of both induction and maintenance treatments, but, on the other, it implied that the first timepoint corresponding to the maintenance phase, and thus useful for the comparative analysis between the two arms, was at 24 weeks. Second, the small patients' numbers could have biased the study results, and, for this reason, we decided to limit our analysis to the 40 weeks timepoint, since afterwards the sample size was too limited to derive reliable results. Third, our results are derived from a study designed with an oxaliplatin-based induction treatment and could not be generalized to an irinotecan-containing first-line therapy, which is not characterized by dose-cumulating adverse events but induces gastro-intestinal and skin toxicity, potentially overlapping with the anti-EGFR class-specific side effects. Moreover, we could not surely translate our findings to the bevacizumab-based treatment strategies and further evidence in this specific setting is needed in order to deepen the investigation upon this topic. Finally, we decided to assess PROs utilizing EORTC QLQ-C30, CR-29 and EQ-5D, based on the results of the previously-reported studies conducted in this setting, but standard guidelines on the optimal tools and measures for QoL analysis are not currently available[13]. In addition, we did not use dermatological QoL measures, aimed at evaluating the psychological and social impact of the anti-EGFRs class-specific skin toxicity, since these measures are poorly used in oncology but could help in better mirroring the real effect on patients' QoL of these drugs[33].

In conclusion, in *RAS* wild-type mCRC patients eligible for modern first-line trials, induction treatment with doublet chemotherapy plus anti-EGFRs is associated with transient but non-negligible QoL deterioration. Treatment de-intensification after an induction phase leads to an overall recovery of health-related QoL, in addition to the expected prevention of oxaliplatin-related neurotoxicity. Further results are needed on this topic both from clinical trials and real-world setting in order to collect robust evidence upon the impact of cancer treatments on patients' QoL and to optimize the therapeutic decision-making algorithm in mCRC patients.

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Figure Legends

Figure 1. Compliance analysis.
In panel A, the rate of patients completing baseline assessments and the assessments at designated time points over the total number of patients eligible and entered into the trial is reported. In panel B, the rate of patients completing completing assessments at designated time points while on study over the total number completing assessment at baseline is depicted. In panel C, the rate of patients completing assessments at designated time points over the number of patients still on study, who were expected to complete questionnaires at each of those time points, is illustrated.

Figure 2. Mean changes from baseline for EORTC QLQ-C30 and EQ-5D VAS in the two treatment arms.
In this figure the mean changes from baseline scores for EORTC QLQ-C30 questionnaire (panels A) and EQ-5D VAS (panel B) in the study population stratified per treatment arm (A versus B, in blue and red, respectively) are depicted.

Figure 3. Mean changes from baseline for EORTC QLQ-C30 and EQ-5D VAS in the overall population.
In this figure the mean changes from baseline scores for EORTC QLQ-C30 questionnaire (panels A) and EQ-5D VAS (panel B) in the overall study population are illustrated.

Figure 4. Best response for global Quality of Life overall.
In this figure the best response for global Quality of Life score of EORTC QLQ-C30 questionnaire in the overall study population is reported, stratifying patients according to the three pre-specified categories (improved, stable and worse).

Supplementary Figure 1. Mean changes from baseline for EORTC QLQ-CR29 in the two treatment arms.
In this figure the mean changes from baseline scores for EORTC QLQ-CR29 questionnaire in the study population stratified per treatment arm (A versus B, in blue and red, respectively) are depicted.

Supplementary Figure 2. Mean changes from baseline for EORTC QLQ-CR29 in the overall population.
In this figure the mean changes from baseline scores for EORTC QLQ-CR29 questionnaire in the overall study population are illustrated.

Supplementary Figure 3. Mean changes from baseline for global Quality of Life according to primary tumor sidedness.
In this figure the mean changes from baseline for global Quality of Life score of EORTC QLQ-C30 questionnaire in patients stratified according to primary tumor sidedness (left versus right, , in blue and red, respectively) are reported.

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