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ORIGINAL ARTICLE

Baseline physical functioning status of metastatic colorectal cancer patients predicts the overall survival but not the activity of a front-line oxaliplatin-fluoropyrimidine doublet

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Abstract

Background. No differences in response rate (RR), progression-free survival (PFS), overall survival (OS) and quality of life (QoL) were seen in patients randomly treated with biweekly oxaliplatin plus either fluorouracil/folinic acid or capecitabine. *Methods.* We investigated the independent effect of baseline clinical characteristics and physical functioning (PF) domain on RR, PFS, and OS in 310 patients who completed the EORTC QLQ-C30 questionnaire. Multivariate analyses stratified by treatment were performed. An exploratory analysis was done by grouping patients with a PF score superior or equal to the highest quartile (n = 111), included between the highest and the lowest quartiles (n = 99), or inferior to the lowest quartile (n = 100). The relationship between these three groups and the ECOG PS was then analysed. *Results.* At multivariate analysis, OS was negatively affected by the number of metastatic sites, the serum alkaline phosphatase, and the ECOG PS, while it was positively affected by the previous surgical resection of the primary tumour. Adding the baseline PF score, the number of disease sites ($p < 0.0001$), the serum alkaline phosphatase ($p = 0.0057$), and the PF ($p = 0.0007$) retained an independent significance, while the ECOG PS and the previous surgery were no longer significant. PF did not significantly affect PFS or RR. A good but not totally overlapping correlation was found between PF grouping and ECOG PS score. *Conclusions.* Baseline self-reported PF independently predicted the OS of patients. Assessment of QoL should be incorporated in randomised trials evaluating the management of patients with MCRC.

Colorectal carcinoma (CRC) is one of the most frequent tumours in Italy and worldwide. In patients with metastatic CRC, chemotherapy has usually a palliative intent, aiming at obtaining a symptoms control, preserving quality of life (QoL), and prolonging overall survival (OS). Until the recent introduction into the clinical practice of targeted therapies, folinic acid (FA)-modulated 5-fluorouracil (5FU) given as i.v. bolus, or as i.v. bolus plus 24-h infusion, either alone or combined with irinotecan or oxaliplatin, represented the standard front-line treatment for this disease. Actually, doublets were reported to significantly increase the response rate (RR), and to prolong the progression-free survival (PFS), in comparison with single-agent FA/5FU, while their impact on OS was controversial [1–7].

In the absence of a significant prolongation of OS, the improvement or preservation, or the delay in deterioration, of quality of life (QoL) may represent a clinically relevant end-point in the management of incurable cancer patients [8,9]. Furthermore, the baseline assessment of QoL may contribute to a comprehensive multi-dimensional evaluation of patients, giving also some prognostic information on their outcome [10,11]. Moreover, the longitudinal evaluation of QoL may help the trade-off between regimens that are unlikely to produce different OS.

Unfortunately, no striking advantage in QoL of patients was noted in trials comparing regimens that were similarly effective [12–16], while a delay in worsening of some specific symptoms [1], or in the global QoL score [2,3], has been reported in favour

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of doublets when compared with single-agent FA/5FU regimens.

We have recently conducted a multicentre randomised phase III trial (SICOG 0401) with the aim of comparing the OS of patients with MCRC treated in first-line with the combination of oxaliplatin plus either FA/5FU (OXAFAFU regimen) or capecitabine (OXXEL regimen) [16]. Prospective assessment and comparison of QoL between arms of treatment was a secondary end-point of this study, and the recruited population had the power to demonstrate a pre-specified clinically meaningful difference in QoL [17,18]. Actually, no differences in RR (33% *vs.* 34%), PFS (median, 6.5 *vs.* 6.6 months) and OS (median, 17.1 *vs.* 16.0 months) were observed between the two arms of this trial. Overall, the OXXEL regimen was better tolerated. Excluding constipation and financial item scores, no other significant differences in single domains, or in global health status, were observed between the two arms during the whole treatment.

Given these results, we planned to investigate the baseline socio-demographic and clinical characteristics of this population, with the aim of ascertain their prognostic value on PFS and OS, and their predictive value on RR. Furthermore, we wondered whether QoL assessment could also add further information to this analysis. In order to avoid false positive results due to multiple testing and multicollinearity, we focused the analysis on the physical functioning (PF) score, because of its possible relationship with the performance status (PS) of patients.

Patients and methods

Three-hundred and twenty-two patients with a histologically proven diagnosis of MCRC were consecutively enrolled in the SICOG trial 0401. Patients selection criteria were previously reported [16]. Informed consent was obtained from all patients, and the trial was approved by the local ethical committee. After stratification for centre, ECOG PS, and previous exposure to adjuvant chemotherapy, patients were randomly allocated to receive either oxaliplatin 85 mg/m^2 i.v. (2-h) on day 1, 6S-FA 250 mg/m^2 i.v. (2-h) followed by 5FU 850 mg/m^2 i.v. (bolus) on day 2 (OXAFAFU arm), or oxaliplatin 100 mg/m^2 i.v. (2-h) and capecitabine 1 000 mg/m^2 orally twice daily from day 1 (evening) to day 11 (morning) (OXXEL arm). Cycles were repeated every two weeks in both arms. QoL was longitudinally assessed using the EORTC Quality of life Questionnaire-Core 30 (EORTC QLQ-C30). All patients were asked to complete this form at registration in the clinic (before physical examination and random assignment), and every two months during treatment (before each planned consultation and disease status assessment). The EORTC QLQ-C30 scores were calculated using the recommended EORTC procedures [19].

Only patients who completed the baseline questionnaire were included in the present analysis. The Kaplan-Meier method estimated the PFS and OS probabilities. Univariate and multivariate analyses were performed for testing the independent relationship of clinical characteristics and PF score with OS, PFS and RR. All tests were stratified by arms of treatment. Baseline socio-demographic characteristics were initially assessed in a univariate model: sex (male *vs.* female), weight loss (<5% *vs.* ≥5% of body weight), primary site (colon *vs.* rectum), previous surgery of the primary (yes *vs.* no), previous adjuvant chemotherapy (yes *vs.* no), and presence of synchronous metastasis (yes *vs.* no) were considered as discrete variables, while age, PS, serum alkaline phosphatase, serum CEA level, and number of disease sites were included as continuous variables. The significant predictors from this univariate analysis were implemented in the multivariate model, and a backward selection was applied to eliminate non-significant parameters. Thereafter, the PF scores of patients, considered as a continuous variable, were added to the model.

For exploratory purpose, the highest and lowest quartile of the distribution of PF score were selected to split the whole population in three numerically comparable groups of patients: those with a score superior or equal to the highest quartile (high score), those with a score inferior to the lowest quartile (low score), and those with a score included between the highest and the lowest quartile (intermediate score). The estimated PFS and OS curves of these three groups were compared with the log-rank test, while their correlation with the ECOG PS score was assessed by means of a Spearman test.

Results

Three hundred and ten of 322 (96%) patients enrolled in SICOG trial 0401 completed the baseline QoL questionnaire and were included in the present analysis. Socio-demographic and clinical characteristics are reported in Table I, according to arm of treatment. It should be noted that, due to absence of upper age-limit for accrual into this trial, 36% patients were ≥ 70 years old. Conversely, only 11 patients had a PS of 2. Fifty-two percent of patients had two or more sites of disease.

Most baseline characteristics were significantly associated with OS at univariate analysis. However, multivariate analysis showed that OS was negatively

Table I. Demographic and clinical characteristics of patients enrolled in the SICOG trial 0401 and assessable for baseline QoL.

Arm	OXAFAFU		OXXEL		TOTAL	
Characteristics	No.	%	No.	%	No.	%
Assessable patients	160	*100*	150	*100*	310	*100*
Males	86	*54*	100	*67*	186	*60*
Females	74	*46*	50	*33*	124	*40*
Median age (range)	65 (37–79)		64 (39–84)		63 (37–84)	
Aged ≥ 70 years	63	*39*	49	*32*	112	*36*
Primary tumor: colon	113	*71*	108	*72*	221	*71*
rectum	47	*29*	42	*28*	89	*29*
Grading: well differentiated	14	*9*	9	*6*	23	*7*
moderately differentiated	90	*56*	97	*65*	187	*61*
poorly differentiated	30	*19*	28	*18*	58	*19*
unknown	26	*16*	16	*11*	42	*13*
Previous surgery	124	*77*	110	*73*	234	*75*
Previous adjuvant chemotherapy	41	*25*	39	*26*	80	*26*
ECOG Performance Status: 0	97	*61*	92	*61*	189	*61*
1	56	*35*	54	*36*	110	*36*
2	6	*4*	5	*3*	11	*3*
No. disease sites: 1	73	*45*	75	*50*	148	*48*
2	52	*33*	42	*28*	94	*30*
3+	35	*22*	33	*22*	68	22
Liver involved	121	*75*	125	*83*	246	*79*
Liver only metastases	48	*30*	62	*41*	110	*35*
Synchronous metastases	93	*58*	86	*57*	179	*57*
Weigh loss ≥ 5%	38	*24*	42	*28*	80	*26*
Alkaline phosphatase > UNL[¶]	59	*37*	51	*34*	110	*35*
CEA value > UNL[¶]	141	*88*	113	*75*	254	*81*
CEA value > 100 ng/mL	38	*24*	32	*21*	70	22

[¶]UNL = upper normal limit

affected only by number of metastatic sites, serum alkaline phosphatase, and PS, while it was positively affected by the previous surgical resection of the primary tumour (Table II). Adding the baseline PF score to the model, the number of disease sites ($p < 0.0001$), the serum alkaline phosphatase ($p = 0.0057$), and the PF ($p = 0.0007$) retained an independent significance, while the PS and the previous surgery were no longer significant (Table III).

OS curves according to baseline PF grouping are plotted in Figure 1. Median OS was 19.3 (95% CI, 17.2 to 21.4) months for 111 patients with a high score, 18.0 (95% CI, 11.2 to 24.8) months for 99 patients with an intermediate score, and 12.1 (95% CI, 9.6 to 14.6) months for 100 patients with a low score. The 1-year probability of survival was 70% (95% CI, 78% to 62%), 61% (95% CI, 71% to 51%), and 51% (95% CI, 61% to 41%), respectively ($p = 0.0012$).

Although several baseline clinical characteristics were associated with PFS at univariate analysis, only the number of metastatic sites ($p = 0.0001$), and the previous weight loss ($p = 0.0329$) retained a significance in the multivariate analysis. PF was not independently related with PFS ($p = 0.7672$). Exploratory analysis on PFS according to PF grouping is showed in Figure 2. PFS was comparable for patients with a high (median, 7.0; 95% CI, 5.6 to 8.4 months) and an intermediate score (median, 6.7; 95% CI, 5.1 to 8.3 months), while it was slightly shorter for patients with a low score (median, 5.5; 95% CI, 4.1 to 6.9 months), but this difference was not significant ($p = 0.1055$).

Table II. Cox analysis of biomedical factors independently affecting OS.

Factors	Wald	HR	95% CI of HR		p-value
Number disease sites	22.18	1.422	1.228	1.647	0.0001
Alkaline phosphatase	9.835	1.300	1.103	1.532	0.0017
Performance status	5.23	1.350	1.046	1.743	0.0123
Surgery of primary	4.29	0.674	0.464	0.979	0.038

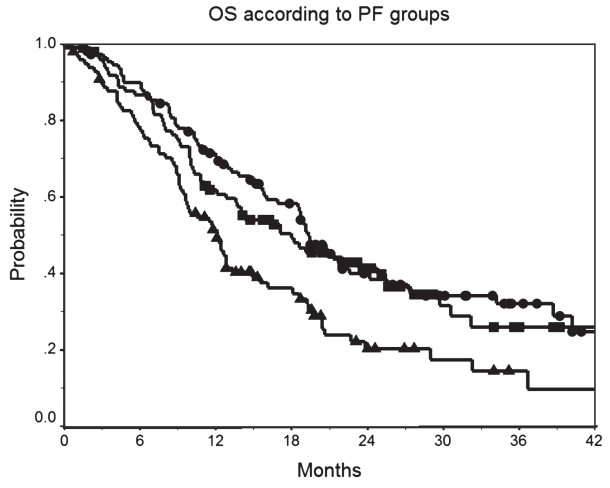

Figure 1. OS curves according to PF score groups: circles, high score (n = 111); squares, intermediate score (n = 99); triangles, low score (n = 100). Log-rank test, p = 0.0012.

Age of patients (p = 0.0001), and presence of synchronous metastases (p = 0.0413) were the only baseline characteristics independently associated with probability of response, while PF showed no correlation with RR. Distribution of responders according to PF grouping is reported in Table IV.

There was a weak but significant correlation (r = 0.426, p = 0.0132) between the PF groups and the PS scores (Table V). However, it should be noted that, among 100 patients in the low PF group, 38 patients were assigned a PS score 0, and 55 patients a PS score 1.

An exploratory analysis showed that 143 of 310 (46.1%) patients received all three active cytotoxic drugs (i.e., fluorouracil or capecitabine, oxaliplatin, and irinotecan) in the course of their disease, and

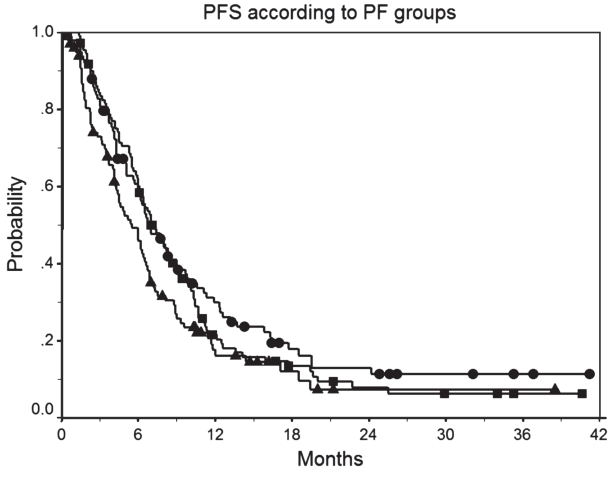

Figure 2. PFS curves according to PF score groups: circles, high score (n = 111); squares, intermediate score (n = 99); triangles, low score (n = 100). Log-rank test, p = 0.1055.

Table III. Cox analysis of factors (including PF score) independently affecting OS.

Factors	Wald	HR	95% CI of HR		p-value
Number disease sites	26.07	1.462	1.264	1.691	0.0001
Alkaline phosphatase	7.66	1.262	1.070	1.489	0.0057
Physical functioning	11.5	0.988	0.981	0.995	0.0007

that these patients lived significantly longer (median, 20.9 months) than patients that did not (median, 11.1 months) (HR = 0.55; 95% CI, 0.41 to 0.73, p = 0.0001). Fifty-eight of 111 patients with a high PF score, 48 of 99 with an intermediate score, and 37 of 100 with a low score received all three active drugs (p = 0.028).

Discussion

This retrospective analysis was conducted to investigate the independent relationship between baseline clinical characteristics and outcome of MCRC patients entered in SICOG trial 0401, and to assess whether the PF score, derived from the EORTC QLQ-C30 questionnaire filled-in by patients, could add further prognostic and/or predictive information.

In this analysis, the PF score was a good prognosticator of OS. Indeed, the Cox analysis confirmed that, besides the number of disease sites, and the serum alkaline phosphatase concentration, the patient-self-reported PF was independently related with OS. It is interesting to note that, when adding this information to the multivariate model, PS of patients was no longer significant, meaning that the former has a greater prognostic value that the latter.

Some hypotheses could be considered to explain this finding. First of all, it is possible that patients could better explicit the perception of their physical status answering to a structured and written questionnaire, which was filled-in before the medical visit, and without third-party conditioning, than by an informal and time-limited conversation with their attending physicians, which is often done in the presence of other people (relatives and/or care-givers). Moreover, a choice within a 4-point-scale may be

Table IV. Relationship between PF grouping and response rate.

Physical functioning group	Responders		
Patients	No.	%	Total
≥ highest quartile	37	33.3	111
< highest and > lowest quartile	36	36.4	99
≤ lowest quartile	31	31.0	100
Total	104	33.5	310

Table V. Relationship between the PF groups and the ECOG PS score.

Physical functioning group	Performance status score						Total
	0		1		2		
Patients	No.	%	No.	%	No.	%	No.
≥ highest quartile	94	84.7	14	12.6	3	2.7	111
< highest and > lowest quartile	57	57.6	41	41.4	1	1.0	99
≤ lowest quartile	38	38.0	55	55.0	7	7.0	100
Total	189	61.0	110	35.5	11	3.5	310

more sensitive than a 3-point score of the PS (it should be remembered that only patients having an ECOG PS ≤ 2 were eligible for the SICOG 0401 trial). Finally, as already shown [20], physicians usually report patients to have fewer problems/symptoms than patients themselves did. As a matter of fact, in our trial only few patients with a low PF score were assigned a PS 2.

Given the lack of statistical relationship between baseline PF and activity of front-line chemotherapy (in terms of RR and PFS), we wondered why it had a negative impact on OS. The exploratory analysis we performed on the salvage treatment after failure of front-line chemotherapy showed that patients treated with all three active drugs in the course of their disease lived significantly longer, and this observation is consistent with previous reports [21,22]. Actually, more than half of patients with high PF, as opposed to about one-third of those with a lower score, received an irinotecan-based salvage treatment, and this difference was highly significant. We suppose that physicians, care-givers, or patients themselves were less willing to embark on a second-line chemotherapy when the patient's physical status was likely worse than that at front-line treatment.

Other investigators have reported the prognostic significance of baseline QoL in MCRC patients [20,23,24], but no insights on the relationship between baseline QoL and activity of front-line chemotherapy, nor with post-progression second-line treatment, have been reported. Earlam et al. [23] investigated the correlation between OS, tumour size, and QoL, assessed with the Sickness Impact Profile (SIP), the Rotterdam symptom checklist (RSC), and the Hospital Anxiety and Depression (HAD) scale, in 50 patients with liver only MCRC. They reported that only the physical score (from the RSC) was independently associated with OS. Maisey et al. [20] examined the EORTC QLQ-C30 questionnaire filled-in by 501 of 631 (79%) patients recruited into four randomized single-centre trials; they found that all domains of QoL, both functioning and symptomatic, with the only exception of the perceived financial impact, were correlated with OS, and the majority of these QoL domains remained independently predictors of OS in the final multivariate model. Lis et al. [24] assessed the quality of life index (QLI) in a consecutive series of 177 patients with CRC cancer in different disease stage. QLI measures global QoL and four major subscales: health and physical functioning, social and economic, psychological/spiritual, and family. They found that health and physical subscale was significantly associated with OS, and this predictive effect was independent of stage and treatment.

On the contrary, Efficace et al. [25], who evaluated QoL by the EORTC QLQ-C30 questionnaire in 299 of 497 (60%) patients enrolled in a 3-arm multicentre randomized trial, reported that social functioning was the only domain retaining significance with OS in the multivariate analysis. Subsequently, this observation has been validated in 443 of 564 (78%) patients enrolled in another multicentre randomized trial carried-out by the same group of investigators [26].

Turja et al. [27] reported the prognostic effect of baseline QoL on 1 253 patients enrolled in the phase III Intergroup N9741 randomized trial. These investigators also reported that a low (below the median value), or a deficient (≤50) baseline QoL score, significantly predicted a shorter OS, independently from baseline PS.

A recent comprehensive critical review has been published on cancer clinical trials that examined the relationship between patient-reported outcomes (PROs), biomedical predictors, and OS. This review retrieved 39 clinical trials carried-out in different type of cancer patients, involving 13 874 subjects. In 36 (92%) of 39 studies, at least one PRO was significantly associated with OS at multivariate analysis. Global QoL and PF each predicted survival more often than other PROs, with significant findings in 15 and 11 studies, respectively [28]. However, although statistically significant, the size of many reported effects was usually small.

In conclusion, PF derived from the EORTC QLQ-C30 questionnaire was not a good predictor for the activity of an oxaliplatin-based front-line chemotherapy in MCRC patients, but it appeared independently associated with OS. Self-reported PF and investigator-assigned PS were not totally overlapping. Therefore, baseline QoL assessment should be incorporated as a stratification factor in future randomized trials comparing new regimens or strategies of treatment, namely when OS is the primary end-point. Its prospective evaluation during and after the treatment on study, together with the information on safety and activity of salvage treatments, could better elucidate the relationship between baseline QoL and OS of patients.

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