Longitudinal quality of life study in patients with metastatic gastric cancer

ORIGINAL ARTICLE

Analysis modalities and clinical applicability of QoL in randomized phase II trial in a digestive oncology

Franck BONNETAIN (1,4), Olivier BOUCHÉ (2), Thierry CONROY (3), Patrick ARVEUX (4), Jean-Luc RAOUL (5), Marc GIOVANNINI (6), Pierre Luc ETIENNE (7), Emmanuel MITRY (8), Jean-François SEITZ (9), Philippe ROUGIER (8), Cécile GIRAULT (1), Laurent BEDENNE (1,10) for the FFCD (Fédération Francophone de Cancérologie Digestive)

(1) INSERM EMI 106/ FFCD ; (2) Centre Hospitalier Universitaire Robert Debré, Reims ; (3) Centre Alexis Vautrin, Vandoeuvre-les-Nancy ; (4) Centre Georges François Leclerc, Dijon ; (5) Centre Eugène Marquis, Rennes ; (6) Institut Paoli Calmettes, Marseille ; (7) Clinique Armoricaine, Saint Brieux ; (8) Centre hospitalier universitaire Ambroise Paré Assistance Publique Hôpitaux de Paris, Boulogne ; (9) Centre Hospitalier Universitaire, La Timone, Marseille ; (10) Centre Hospitalier Universitaire le Bocage ; Dijon and FFCD, Faculté de Médecine, 21079 Dijon Cedex.

SUMMARY

Objectives — The aim of this study was to compare the longitudinal quality of life (QoL) between LV5FU2-irinotecan and LV5FU2 alone or LV5FU2-cisplatin in a randomized Phase II trial in patients with metastatic gastric adenocarcinoma.

Methods — Among 134 eligible patients, QLQ-C30 scores were collected and described at each 2 monthly follow-up visit during 6 months. The frequencies of QLQ-C30 score improvement were calculated and mixed models for repeated measurements were applied with or without extreme poorest imputation for missing scores. The "survival" until definitive global health score (GHS) deterioration was estimated.

Results — At the 3rd follow-up, patients with a stable or improved global health ranged from 11% in the LV5FU2-cisplatin arm to 18% in the LV5FU2-irinotecan arm. The irinotecan-based-therapy presented 14 to 15 scores with a better QoL. The time until definitive GHS deterioration was globally similar between treatment arms.

Conclusion — This study highlights a better impact of LV5FU2-irinotecan and the interest of QoL assessment in phase II trials to complement the risk-benefit judgement.

RÉSUMÉ

Analyse longitudinale de la qualité de vie auprès de malades ayant un cancer métastatique de l'estomac. Intérêts et modalités d'analyse de la qualité de vie dans un essai randomisé de phase II en oncologie digestive

Franck BONNETAIN, Olivier BOUCHÉ, Thierry CONROY, Patrick ARVEUX, Jean-Luc RAOUL, Marc GIOVANNINI, Pierre Luc ETIENNE, Emmanuel MITRY, Jean-François SEITZ, Philippe ROUGIER, Cécile GIRAULT, Laurent BEDENNE for the FFCD (Fédération Francophone de Cancérologie Digestive)

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Objectifs — Analyser longitudinalement la qualité de vie (QdV) de malades ayant un adénocarcinome gastrique métastatique dans un essai randomisé de phase II comparant LV5FU2-irinotecan, LV5FU2 et LV5FU2-cisplatine.

Méthodes — Les scores de QdV du QLQ-C30 ont été recueillis à chaque fin de cycle durant 6 mois auprès des 134 malades éligibles. La fréquence des malades présentant une amélioration de leur QdV à 6 mois a été calculée pour chacun des scores du QLQ-C30. Des modèles mixtes d'analyse de variance pour mesures répétées ont été réalisés et la « survie » jusqu' à détérioration définitive du score de santé globale (GHS) a été estimée.

Résultats — Après 3 suivis, les malades présentant une amélioration du GHS varient de 11% dans le bras LV5FU2-cisplatin à 18 % dans le bras LV5FU2-irinotecan. Comparativement aux autres traitements, les moyennes de 14 à 15 scores du QLQ-C30 sont plus élevées dans le bras irinotecan. Le temps jusqu'à détérioration définitive du GHS est globalement semblable selon les chimiothérapies.

Conclusion — Cette étude suggère un meilleur impact de l'association LV5FU2-irinotecan et souligne l'intérêt d'une analyse adaptée de la QdV dans un essai de phase II en oncologie digestive.

Introduction

Gastric cancer represents the second most common cause of cancer mortality worldwide with overall 5-year survival rates ranging from 10% to 15% [1]. Surgery is potentially the only curative treatment for localized gastric cancer, but most cases present at an advanced stage. Irinotecan is a cytotoxic agent with promising activity in combination with 5-FU in gastrointestinal cancers [2-6]. The Federation Francophone de Cancérologie Digestive (FFCD) phase II trial was designed to compare LV5FU2 alone or in combination with cisplatin or irinotecan in patients with an untreated metastatic gastric cancer [7]. The results have showed that irinotecan is the most promising regimen for a future phase III trial with a better overall response rate [7].

In palliative settings, treatment selection should also be based on perceived health-related quality of life (QoL) describing the impact of disease and treatment on patient's ability to lead a fulfilling life [8-16].

While the aims of QoL assessment and their analyses have been well standardized in phase III cancer clinical trials, its place remains controversial in phase II trials [17-19]. Some authors have stated that QoL measurement is unnecessary or unlikely to be relevant to most phase II trials [11, 14, 20, 21].

Reprints: F. BONNETAIN, INSERM EMI 106 and Federation Francophone de Cancerologie Digestive, Faculty of Medicine, 7 Bd Jeanne d'Arc, BP 879000, 21079 Dijon cedex.
E-mail : FBonnetain@dijon.fnclcc.fr

However, QoL could be incorporated in the following settings [12,13,21,22] : trials where the treatments are not likely to influence long-term survival but might improve palliation ; phase II trials assessing the activity of new agents in poorly responsive malignant lesions ; information about QoL can complement data to selected agents for testing in phase III trials. It may still be useful to pilot QoL instruments before being used in a Phase III study. Investigators can ensure that the instrument covers all the relevant issues and test the infrastructure for future data collection [21,22]. Interventions may then be required in a phase III study to minimize symptoms and to optimize data collection [22].

Due to sample size limitation, QoL analyses should be performed in a different way than in a phase III trial. However, we didn't find any specific guidelines related to QoL study in phase II trial. From our point of view, it seemed interesting to explore the interest of QoL assessment in a phase II study by investigating analysis modalities and their clinical applicability. The main objective of this study was to compare the longitudinal QoL of metastatic gastric cancer patient according to irinotecan based — therapy and other treatments.

Patients and methods

Patients

The study was performed according to the Declaration of Helsinki and the Good Clinical Practice guidelines and was approved by an Ethics Review Committee. All patients provided written informed consent before inclusion. Eligible patients had an histological-proven metastatic adenocarcinoma, a measurable metastatic disease, no symptomatic brain metastases, an age between 18 and 75 years, and a World Health Organization performance status (WHO PS) Ω2 with life expectancy of more than 2 months. The main exclusion criteria were chronic diarrhoea, prior enteropathy or extensive intestinal resection.

Study design and randomization

The study was an open-label multicenter phase II randomized trial. Eligible patients were randomized between 3 arms: - LV5FU2; - LV5FU2 + cisplatin; LV5FU2 + irinotecan. Stratification was performed according to the institution, tumor site (cardia/other localization), prior adjuvant chemotherapy (yes/no) and WHO PS (0 *vs* 1/2). In the week preceding treatment, patients underwent a complete medical history, a physical examination and a QoL evaluation.

Chemotherapy administration and dose adjustments

Patients assigned to the LV5FU2 arm received LV 200 mg/m^2 over 2 hours followed by 5-FU 400 mg/m^2 bolus then a 600 mg/m^2 continuous infusion of 5-FU over 22 hours on days 1 and 2, repeated every 14 days. No prophylactic premedication was given. Patients assigned to the LV5FU2-cisplatin arm received: cisplatin 50 mg/m^2 over 1 hour on day 1 or day 2 with LV5FU2. Prophylactic medication consisted of antiemetics and 120 mg methylprednisolone 10 minutes before cisplatin, hydration (1 L over 3 hours before and after cisplatin), oral antiemetics and corticosteroids from day 2 to day 5. Patients assigned to the LV5FU2-irinotecan arm received Irinotecan 180 mg/m^2 IV over 90 minutes on day 1 with LV5FU2.

The treatment was continued for at least 4 cycles or until disease progression, unacceptable toxicity, patient refusal or physician decision to withdraw patients. Patients showing a complete response received treatment for up to one year. All adverse events were graded using the WHO Toxicity Criteria

Quality of life

Patients were requested to complete the EORTC Quality-of-Life Core Questionnaire (QLQ-C30) before randomization and every 2 months (at the end of each cycle) until treatment discontinuation [23]. The QLQ-C30 was proposed and collected in the waiting room before the medical consultation. The QLQ-C30 was developed to assess the QoL of cancer patients in clinical trials [24-26]. It consists of 30 items, among which 24 are aggregated into 9 dimensions: 5 functional dimensions (physical, role, cognitive, social, and emotional), 3 symptom dimensions (nausea, pain, fatigue) and a global health dimension. The 6 other single items scale evaluated symptoms: dyspnea, difficulty in sleeping, anorexia, constipation, diarrhoea and perceived financial difficulties [23]. After checking data validity, the scoring of the questionnaire was performed according to EORTC guidelines [27]. The functional and global scores range from 0 (worse) to 100 (best) and symptom scores from 0 (best) to 100 (worse).

Statistical analysis

The expected number of patients for this study was initially calculated according to an Ensign-MiniMax optimal three-stage design with 0.05 alpha and 0.1 beta levels [28]. A sample of 45 patients per arm was necessary [7]. Analyzes were realized on an intent-to-treat principle with BMDP and Stata 8 statistical software.

Descriptive analysis

The main clinical variables were compared at inclusion. The frequencies of treatment discontinuation were described at each follow-up. The missing QoL data were analyzed by calculating: — the rate of QLQ-C30 completion in patients with follow-up (observed/ expected); — and as example the rate of Global health scores completion. In order to investigate non-random missing QoL, the rate of QLQ-C30 completion was also calculated according to treatment discontinuation and progression [29, 30]. Finally, we have decided to focus on QoL study until the 3rd follow-up where the questionnaires completion rates were about 50%. The available QoL scores and delays in QLQ-C30 assessment were described as a mean, standard deviation (SD) at baseline and at each 2 monthly follow-up visit during 6 months. Pre-study scores were compared between treatments arms using the analysis of variance (Bonferroni adjustment for multiple comparisons). We have reported graphically the mean of available Global health and diarrhea scores at each follow-up [31]. According to tumor progression, the mean (SD) of global health score was also described.

At baseline and the 3rd follow-up visit the main components associated with the perceived global health were explored by calculating a Spearman coefficient correlation between the global health score and: — the other 14 QLQ-C30 scores [32]; — the number and maximal toxicity grades reported during the cycle (diarrhea, nausea/vomiting, neutropenia, anemia, infection and alopecia) [22]. A relevant association was retained when the correlation coefficient was greater or equal to ∂ 0.5.

Longitudinal analysis

Firstly, in each arm we have reported the rate of patients having an improved QLQ-C30 score (any positive change) or stable between inclusion and the 3rd follow-up among all baseline eligible patients and among patients with available scores. Secondly, during a 6-month follow-up, a mixed model analysis of variance for repeated measurements was performed [33-35] : — to analyze the longitudinal change whatever the treatment arm ; — to estimate the adjusted mean differences in QoL scores between irinotecan and the other treatments whatever the follow-up. In order to perform sensitivity analyses about missing scores, the same mixed models were performed imputing the poorest QoL score in patients with follow-up [36, 37] : 0 for the functional and global health scales and 100 for the symptom scales. Finally, using a Kaplan-Meier estimate we have calculated the probability of "survival" until definitive global health score deterioration during treatment representing the time between baseline and the time of the first score deterioration without any QoL improvement or any available QoL data thereafter.

Results

Patient characteristics

One hundred and thirty-six patients were enrolled between January 1999 and October 2001 in 41 French centers. One

Table I. – Patients characteristics.
Description des caractéristiques cliniques des malades.

	LV5FU2	LV5FU2-Cisplatin	LV5FU2-Irinotecan
No. of patients	**45**	**44**	**45**
Sex :			
Male (%)	82	80	84
Age, years			
Median (range)	64 (45-75)	64 (43-76)	65 (37-76)
WHO performance status (%)			
0 or 1	76	75	78
2	24	25	22
Primary tumor location (%)			
Cardia	29	30	33
Gastric	71	70	67
Symptom (%)			
Weight loss No/<10%/>10%	20 / 49 / 27	27 / 34 / 32	29 / 18 / 51*
Anorexia : Yes	47	50	33
Dysphagia : Yes	24	18	16
Pain : Yes	51	43	38
		Main clinical outcomes	
Overall response [95% CI]	6 (13%) [3.4-23.3]	12 (27%) [14.1-40.4]	18 (40%) [25.7-54.3]
Median OS [95% CI], months	6.8 [2.6-11.1]	9.5 [6.9-12.2]	11.3 [9.3-13.3]
Median PFS [95% CI], months	3.2 [1.8-4.6]	4.9 [3.5-6.3]	6.9 [5.5-8.3]
Median no. of cycles (range)	7 (1-20)	7 (1-18)	10 (1-25)
No. of cycles delayed for toxicity (%)	12 (3%)	45 (13%)	28 (6%)
		Grade ¾ toxicity according to WHO grade	
Hematologic toxicity	22%	71%	44%
• Neutropenia	11%	61%	40%
• Febrile neutropenia∂infection	9%	18%	11%
• Anemia	16%	30%	16%
• Thrombocytopenia	2%	2%	0%
Gastrointestinal toxicity	18%	25%	33%
• Nausea/vomiting	11%	23%	9%
• Diarrhea	2%	2%	22%
• Stomatitis	4%	0%	7%
Other toxicity			
• Alopecia	0%	0%	13%
• Cutaneous	2%	5%	0%
• Neurosensory	0%	5%	0%
• Cardiac	0%	0%	2%

Abbreviations: WHO, World Health Organization.
* The number of patients with weight loss >10% was higher in the LV5FU2-irinotecan arm compared with the other two arms (p = 0.05). OS: Overall survival. PFS: Progression Free Survival.
Abréviations : OMS, Organisation Mondiale de la Santé
** Nombre de malades ayant une perte de poids >10% est supérieur dans le bras LV5FU2-irinotecan comparativement aux deux autres chimiothérapie (p=0.05). OS: Survie Globale. PFS: Survie sans progression.*

Table II. – Follow-ups and patterns of QLQ-C30 completion at each follow-up according to treatment discontinuation and arms.
Description des malades ayant été suivis et des causes de données manquantes du QLQ-C30 selon le bras de traitement et l'arrêt de la chimiothérapie.

	LV5FU2	LV5FU2-Cisplatin		LV5FU2-Irinotecan					
	N	QLQ-C30 completion N (%)	Timing of QoL assessment Mean (SD)	N	QLQ-C30 completion N (%)	Timing of QoL assessment Mean (SD)	N	QLQ-C30 completion N (%)	Timing of QoL assessment Mean (SD)
N° follow-up:									
— Baseline	45	40 (89%)		44	40 (91%)		45	41 (91%)	
— 1 (– 2 months)	43	32 (74%)	1.9 (0.2)	42	31 (74%)	2.5 (1.2)	43	32 (72%)	2.1 (0.5)
— 2 (– 4 months)	26	16 (62%)	3.6 (0.6)	35	15 (43%)	3.7 (0.7)	35	21 (60%)	4.0 (0.8)
— 3 (– 6 months)	22	12 (55%)	5.3 (0.4)	21	8 (38%)	6.3 (2.2)	29	17 (59%)	5.9 (1.0)
— 4 (– 8 months)	8	3 (38%)	8.5 (0.4)	10	4 (40%)	7.4 (2.2)	16	8 (50%)	7.7 (2.2)
— 5 (– 10 months)	6	2 (33%)	9.7 (2.5)	1	1 (100%)	—	7	3 (43%)	8.3 (2.1)
— 6 (– 12 months)	1	0 (0%)	—	0	—	—	5	1 (20%)	—
			Global health score Mean (SD)			Global health score Mean (SD)			Global health score Mean (SD)
1ST FOLLOW-UP									
Treatment discontinuation:									
— Yes	15	8 (53%)	50.0 (20.4)	5	1 (20%)	83.3(-)	9	6 (67%)	61.7 (20.1)
— No	28	24 (86%)	69.9 (18.9)	37	30 (81%)	66.0 (25.8)	34	25 (74%)	68.3 (21.8)
Tumor progression:									
— Yes	14	8 (57%)	50.0 (24.1)	7	3 (43%)	69.4 (17.3)	10	5 (50%)	50.0 (16.7)
— No	26	22 (84%)	70.6 (18.6)	31	25 (81%)	65.5 (27.7)	31	25 (81%)	70.8 (20.0)
2ND FOLLOW-UP:									
Treatment discontinuation :									
— Yes	4	2 (50%)	54.2 (5.9)	13	4 (31%)	75.0 (8.3)	6	0 (0%)	41.2 (-)
— No	22	14 (64%)	65.1 (25.2)	22	11 (50%)	70.0 (25.5)	29	21 (72%)	68.4 (22.5)
Tumor progression:									
— Yes	6	4 (67%)	54.2 (17.3)	10	5 (50%)	64.6 (21.9)	7	1 (14%)	41.7 (-)
— No	18	11 (61%)	65.6 (26.5)	20	9 (45%)	74.1 (23.4)	27	20 (74%)	68.1 (23.1)
3RD FOLLOW-UP:									
Treatment discontinuation :									
— Yes	14	7 (50%)	72.2 (19.5)	13	3 (23%)	55.6 (50.9)	12	6 (50%)	40.0 (10.9)
— No	8	5 (63%)	38.9 (9.6)	8	5 (63%)	71.7 (27.4)	17	11 (65%)	71.3 (20.0)
Tumor progression:									
— Yes	15	8 (53%)	66.7 (23.1)	10	2 (20%)	100 (0.0)	9	4 (44%)	54.2 (17.7)
— No	6	4 (67%)	41.7 (11.8)	8	6 (75%)	54.2 (33.2)	19	13 (68%)	61.2 (24.2)

SD: Standard Deviation

Table III. – Mean and number of available QLQ-C30 scores at baseline and the 3[rd] follow-up.
Moyennes et nombre de questionnaires QLQ-C30 complétés à l'inclusion et au 3[e] suivi.

	QLQ-C30 Scores :	LV5FU2				LV5FU2-Cisplatin				LV5FU2-Irinotecan			
		Mean (SD)	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)	N
		Baseline		3rd follow-up		Baseline		3rd follow-up		Baseline		3rd follow-up	
Functional scales:	Global Health	52.3 (26)	37	61.1 (23)	9	52,8 (27)	33	65.6 (35)	8	55.7 (25)	38	60.1 (23)	14
	Physical	77.8 (22)	38	69.7 (14)	11	74.4 (25)	35	86.7 (10)	8	79.0 (16)	40	80.5 (13)	14
	Role	58.3 (34)	38	66.7 (33)	11	64.7 (35)	34	75.0 (28)	8	63.8 (33)	40	78.6 (18)	14
	Emotional	59.4 (29)	37	75.0 (20)	10	63.7 (28)	34	83.3 (20)	8	72.4 (23)	38	76.2 (19)	14
	Cognitive	73.4 (25)	37	70.0 (31)	10	82.4 (22)	34	81.3 (23)	8	85.1 (19)	37	82.1 (19)	14
	Social	57.9 (33)	36	65.0 (34)	10	66.7 (34)	33	75.0 (28)	8	61.1 (33)	36	78.6 (18)	14
Symptom scales:	Fatigue	55.1 (28)	38	45.5 (24)	11	45.4 (32)	34	29.2 (21)	8	40.2 (28)	39	38.1 (20)	14
	Nausea	28.9 (29)	38	9.1 (14)	11	17.2 (28)	34	25.0 (22)	8	10.7 (24)	39	13.1 (18)	14
	Pain	39.9 (34)	38	13.6 (18)	11	41.4 (34)	35	20.8 (25)	8	29.2 (30)	40	20.2 (23)	14
	Dyspnoea	24.6 (27)	38	33.3 (30)	11	15.2 (24)	33	29.2 (33)	8	21.9 (28)	38	21.4 (21)	14
	Insomnia	46.5 (38)[P]	38	9.1 (16)	11	36.3 (32)[P]	34	12.5 (17)	8	23.9 (32)[P]	39	16.7 (17)	14
	Appetite loss	50.9 (42)	38	30.3 (32)	11	41.9 (40)	35	16.7 (25)	8	36.8 (40)	39	16.7 (29)	14
	Constipation	39.5 (38)[J]	38	18.2 (35)	11	17.7 (25)[J]	34	16.7 (18)	8	17.1 (25)[J]	39	16.7 (29)	14
	Diarrhoea	19.3 (29)	38	12.1 (23)	11	17.7 (22)	34	16.7 (25)	8	8.6 (21)	39	11.9 (17)	14
	Financial	10.8 (25)	37	0.0 (0.0)	10	9.1 (15)	33	14.3 (26)	7	6.3 (13)	37	11.9 (21)	14

Scores vary from 0 (worse) to 100 (best) for functional and global health scale and from 0 (best) to 100 (worse) for symptoms scales. ☆ : p Bonferroni< 0.05. ✪ : p Bonferroni< 0.01. SD: standard deviation.
Les scores du QLQ-C30 varient de 0 (pire) à 100 (meilleure) pour les dimensions fonctionnelles et de santé globale ; de 100 (pire) à 0 (meilleure) pour les dimensions symptomatiques.

patient with a lymphoma and another without metastatic disease were ineligible. The 134 eligible patients had received treatment allocated by randomization. The main clinical characteristics were similar (table I). The major toxicity was hematological, which was highest in the cisplatin regimen and lowest for LV5FU2. Gastrointestinal toxicity was common with nausea/vomiting experienced by more patients in the LV5FU2-cisplatin arm, and with diarrhea experienced by more patients in the LV5FU2-irinotecan arm (table I).

Quality of life

Follow-up, treatment discontinuation and missing data

According to baseline, the rate of patients performing the 3rd follow-up ranged from 48% in LV5FU2-cisplatin arm to 64% in the Irinotecan arm (table II). The major reason for stopping treatment was disease progression: 37 (82%) in LV5FU2, 24 (54.5%) in cisplatin and 27 (60%) in irinotecan arms. The QLQ-C30 completion rate was of about 90% at baseline (table II). At the 3rd follow-up the completion rates were 55% (N = 12) in LV5FU2, 38% (N = 8) in cisplatin and 59% (N = 17) in irinotecan arms. Completion rates were systematically higher in patients who did not stop treatment at follow-up (table II). Excepted in the LV5FU2 and cisplatin arm, the global health score was overall better among patients with no tumor progression (table II).

Description of QLQ-C30 scores during follow-up

At baseline, insomnia and constipation symptoms scores were significantly lower in the irinotecan arm than in the other arms ($p < 0.05$) (table III). Global health scores were globally similar between arms during follow-up: increasing until the first follow-up and then decreasing until the 3rd follow-up though superior to baseline scores (figure 1). During the follow-up, the diarrhea score was globally lower in the irinotecan regimen (figure 2).

Correlation between global health score and other QLQ-C30 scores

At baseline, the main QLQ-C30 scales associated with global health were role, social emotional and physical functioning (table IV). While nausea, constipation and diarrhea affected QoL, the major symptoms affecting global QoL were: fatigue, pain, insomnia and loss of appetite. At the third follow-up,

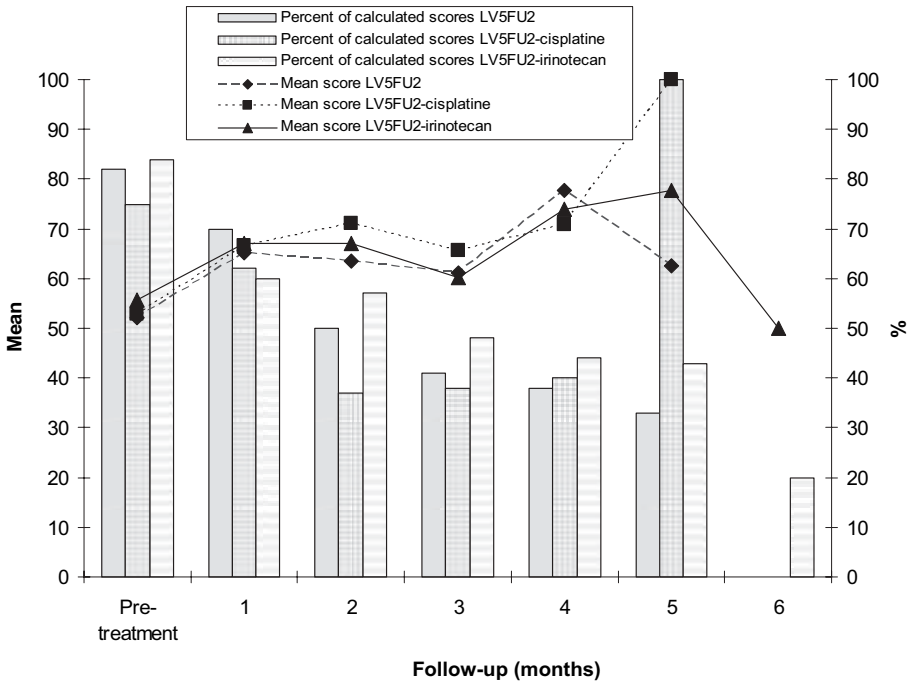

Fig. 1 – Means of Global health score and rates of available scores during follow-up according to treatment arms.
Scores vary from 0 (worse) to 100 (best).
Moyennes du score de santé globale et taux de scores renseignés selon la chimiothérapie à chaque suivi.
Le score de santé globale varie de 0 (pire) à 100 (meilleure).

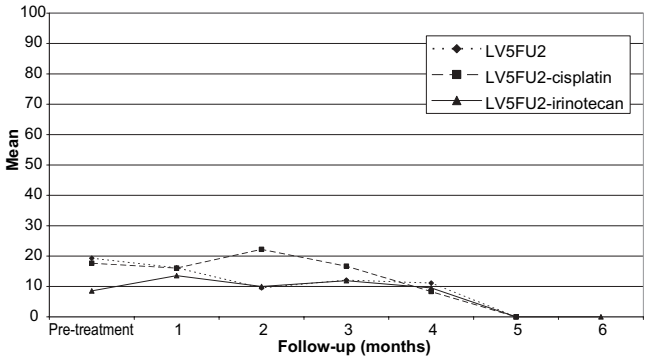

Fig. 2 – Means of Diarrhea score during follow-up according to treatment arms.
Scores vary from 100 (worse) to 0 (best).
Moyennes du score de symptômes diarrhéiques a chaque suivi selon le bras de traitement.
Le score de symptômes diarrhéiques varie de 100 (pire) à 0 (meilleure).

except for emotional scale in the LV5FU2 and cisplatin arms, and physical functioning in irinotecan arm all the others functional scales influenced global health scores (table IV). Fatigue and pain remained the major symptoms influencing global QoL in each arm. Loss of appetite and insomnia affected global QoL in LV5FU2 and LV5FU2-cisplatin arms, respectively (table IV).

Correlation between reported clinical toxicities and Global health scores

At the 1st follow-up, the number and the maximal grade of diarrhea were correlated: - positively in the LV5FU2 regimen ($r = 0.37$/ $r = 0.35$; $P < 0.05$), — negatively in the irinotecan regimen ($r = - 0.42$/ $r = - 0.39$; $P < 0.05$). At the 2nd follow-up, the number of nausea, of total reported toxicities and maximal grade of diarrhea were respectively correlated with LV5FU2 ($r = - 0.46$; $P < 0.05$), cisplatin ($r = - 0.54$; $P < 0.05$) and irinotecan regimen ($r = - 0.48$; $P < 0.05$). At the 3rd follow-up, the number and the maximal grade of alopecia ($r = - 0.79$/ $r = - 0.78$; $P < 0.05$) were negatively associated with global health score in cisplatin arm. The anemia toxicity grade was correlated with global health score in the irinotecan regimen ($r = - 0.54$; $P < 0.05$).

Frequencies of patients with improved or stable QLQ-C30 scores between baseline and the 3rd follow-up

Patients presenting an improved or a stable global health score at the 3rd follow-up were more frequent in the irinotecan arm: 13% in LV5FU2 arm, 11% in LV5FU2-cisplatin arm and 18% in LV5FU2-irinotecan arm (table V). Apart from emotional, pain and insomnia the other QLQ-C30 scores improvements were by decreasing order more frequent in the irinotecan, LV5FU2 and cisplatin arms (table V). Among patients with available QoL scores, functional scores improvement was less frequent in the irinotecan regimen.

Mixed model analysis of variance for repeated measurements

The global health, role, emotional, social, pain, sleep and appetite scores were significantly improved after 6 months of chemotherapy (table VI). Whatever the follow-up, the Global health and the 5 functional scores were higher in irinotecan compared to the LV5FU2 arm. There was also an apparent difference in the symptom scores: 8 symptom scores were lower in the irinotecan arm (table VI). According to the cisplatin arm, the irinotecan-based therapy was associated with a higher global QoL, 5 functional scores (table VI) and 8 less symptom scores.

Table IV. – Spearman Correlation coefficient between QLQ-C30 scores and Global Health score according to treatment arm at baseline and the 3rd follow-up.

Coefficients de corrélation de Spearman entre le score de santé globale et les autres dimensions du QLQ-C30 à l'inclusion et au 3e suivi selon le bras de traitement.

			LV5FU2		LV5FU2-Cisplatin		LV5FU2-Irinotecan	
QLQ-C30 Scores :			r	P	r	P	r	P
Baseline	Functional scales:	Physical	0.4	< 0.01	0.6	< 0.001	0.6	< 0.001
		Role	0.6	< 0.001	0.7	< 0.001	0.6	< 0.001
		Emotional	0.4	< 0.05	0.5	< 0.01	0.4	< 0.01
		Cognitive	0.1		0.3		0.2	
		Social	0.6	< 0.001	0.7	< 0.001	0.6	< 0.001
	Symptom scales:	Fatigue	- 0.6	< 0.001	- 0.7	< 0.001	- 0.7	< 0.001
		Nausea	- 0.2		- 0.5	< 0.01	- 0.4	< 0.05
		Pain	- 0.6	< 0.001	- 0.6	< 0.001	- 0.6	< 0.001
		Dyspnoea	- 0.2		- 0.1		- 0.5	< 0.01
		Insomnia	- 0.4	< 0.05	- 0.5	< 0.01	- 0.6	< 0.001
		Appetite loss	- 0.6	< 0.001	- 0.6	< 0.001	- 0.7	< 0.001
		Constipation	- 0.4	< 0.01	- 0.4	< 0.05	- 0.3	< 0.05
		Diarrhoea	- 0.2		- 0.5	< 0.01	- 0.4	< 0.05
		Financial	- 0.2		- 0.1		0.1	
3rd Follow-up	Functional scales:	Physical	0.7	< 0.05	0.6		0.0	
		Role	0.6		0.8	< 0.05	0.7	< 0.01
		Emotional	0.4		- 0.4		0.7	< 0.01
		Cognitive	0.6		0.6		0.5	< 0.05
		Social	0.6		0.8	< 0.05	0.7	< 0.01
	Symptom scales:	Fatigue	- 0.7	< 0.05	- 0.5		- 0.7	< 0.01
		Nausea	- 0.1		- 0.3		- 0.3	
		Pain	- 0.6		- 0.7		- 0.6	
		Dyspnoea	0.2		0.2		- 0.2	
		Insomnia	- 0.1		0.6		- 0.4	
		Appetite loss	- 0.6		0.0		- 0.3	
		Constipation	- 0.4		- 0.4		- 0.1	
		Diarrhoea	0.3		- 0.1		- 0.1	
		Financial	0.0		0.1		- 0.1	

Scores vary from 0 (worse) to 100 (best) for functional and global health scale and from 0 (best) to 100 (worse) for symptoms scales. r, spearman correlation coefficient, significant if P ¢ 0.05.

Les scores du QLQ-C30 varient de 0 (pire) à 100 (meilleure) pour les dimensions fonctionnelles et de santé globale ; de 100 (pire) à 0 (meilleure) pour les dimensions symptomatiques.

. r, coefficient de corrélation de Spearman significatif si P Ω0.05.

Table V. – Description of the QLQ-C30 scores stable or improved at the third follow-up according to treatment arm.

Description de la fréquence des malades présentant un score de qualité de vie amélioré ou maintenu au 3e suivi selon le bras de traitement.

		LV5FU2 N = 45			LV5FU2-Cisplatin N = 44			LV5FU2-Irinotecan N = 45		
	QLQ-C30 Scores at the third follow-up ∅Baseline (N total ☤):	**N**	%	%*	**N**	%	%*	**N**	%	%*
Functional scales:	— Global health (8/6/13)	**6**	13.0	75.0	**5**	11.0	83.0	**8**	18.0	62.0
	— Physical (10/6/14)	**6**	13.0	60.0	**4**	9.0	67.0	**7**	16.0	50.0
	— Role (10/6/14)	**5**	11.0	50.0	**3**	7.0	50.0	**11**	24.0	79.0
	— Emotional (9/6/13)	**8**	18.0	89.0	**6**	14.0	100.0	**7**	16.0	54.0
	— Cognitive (9/6/13)	**6**	13.0	67.0	**4**	9.0	67.0	**7**	16.0	54.0
	— Social (8/6/13)	**4**	9.0	50.0	**3**	7.0	50.0	**10**	22.0	77.0
Symptom scales:	— Fatigue (10/6/14)	**4**	9.0	40.0	**3**	7.0	50.0	**8**	18.0	57.0
	— Nausea (10/6/14)	**7**	16.0	70.0	**1**	2.0	17.0	**8**	18.0	57.0
	— Pain (10/6/14)	**7**	16.0	70.0	**4**	9.0	67.0	**7**	16.0	50.0
	— Dyspnoea (10/6/13)	**7**	16.0	70.0	**3**	7.0	50.0	**9**	20.0	70.0
	— Insomnia (10/6/14)	**10**	22.0	100.0	**6**	14.0	100.0	**10**	22.0	71.0
	— Appetite loss (10/6/13)	**9**	20.0	90.0	**5**	11.0	83.0	**11**	24.0	85.0
	— Constipation (10/6/14)	**8**	18.0	80.0	**4**	9.0	67.0	**12**	27.0	86.0
	— Diarrhoea (10/6/14)	**9**	20.0	90.0	**4**	9.0	67.0	**10**	22.0	71.0
	— Financial (10/6/13)	**9**	20.0	100.0	**4**	9.0	67.0	**10**	22.0	77.0

%* Rate of QLQ-C30 score stable or improved between baseline and the 3rd follow-up among available scores at these 2 time points. ☤ Number of patients with available scores at baseline and the 3rd follow-up. Scores vary from 0 (worse) to 100 (best) for functional and global health scale and from 0 (best) to 100 (worse) for symptoms scales.

%: Pourcentage de patients ayant un score QLQ-C30 maintenu ou amélioré entre l'inclusion et le 3ème suivi parmi les patients ayant ces scores renseignés. ☤ : Nombre de patients ayant le score QLQ-C30 renseigné à l'inclusion et au 3ème suivi.*

Les scores du QLQ-C30 varient de 0 (pire) à 100 (meilleure) pour les dimensions fonctionnelles et de santé globale ; de 100 (pire) à 0 (meilleure) pour les dimensions symptomatiques.

The only exception was for lower dyspnea in patients receiving cisplatin.

Poorest score imputation

While QLQ-C30 scores significantly decreased during follow-up, the QLQ-C30 missing scores imputation confirmed that during 6 months, the irinotecan-based therapy was associated respectively with 15 and 14 scales having a better QoL level than cisplatin and LV5FU2 (table VI).

Kaplan-Meier methods to analyse longitudinal quality of life

The survival until global health score deterioration was better in the LV5FU2-cisplatin arm until 6 months. Thereafter, patients presenting a global health score deterioration at 6 months were 63% [38 – 87], 56% [30 – 85] and 53% [34 – 73] in LV5FU2, LV5FU2-cisplatin and LV5FU2-irinotecan arms, respectively (figure 3). The median time until definitive global health score deterioration was: 5.5 months in the LV5FU2 and LV5FU2-cisplatin arms and 5.8 in the LV5FU2-irinotecan arm, respectively.

Table VI. – Longitudinal QoL analysis according to treatment arm using mixed model analysis of variance for repeated measurement.

Analyse longitudinale de la qualité de vie selon le bras de traitement par un modèle mixte d'analyse de variance pour mesures répétées.

		Time effect*	Treatment Effect	LV5FU2-Irinotecan vs LV5FU2	LV5FU2-Irinotecan vs LV5FU2-Cisplatin
	QLQ-C30 Scores :	P	P	Mean differences	Mean differences
Functional scales:	Global health	< 0.0001	0,89	+ 2,2	+ 0,8
	Physical	0.45	0.41	+ 2.4	+ 4.9
	Role	< 0.01	0.68	+ 4.6	+ 3.7
	Emotional	< 0.0001	0.29	+ 4.1	+ 6.7
	Cognitive	0.79	0.15	+ 8.3	+ 2.6
	Social	< 0.01	0.71	+ 4.7	+ 2.5
Symptom scales:	Fatigue	0.16	0.12	- 10.2	- 4.4
	Nausea	0.99	0.55	- 2.6	- 4.7
	Pain	< 0.0001	0.72	- 1.1	- 3.9
	Dyspnoea	0.36	0.17	- 3.5	+ 5.2
	Insomnia	< 0.0001	0.13	- 10.1	- 8.2
	Appetite loss	< 0.01	0.31	- 8.8	- 8.1
	Constipation	0.41	< 0.05	- 11.9	- 0.3
	Diarrhoea	0.97	0.27	- 4.7	- 5.9
	Financial	0.36	0.72	+ 2.1	- 0.5
		Poorest QLQ-C30 allocation for missing scores			
		Time effect*	**Treatment Effect**	**LV5FU2-Irinotecan *vs* LV5FU2**	**LV5FU2-Irinotecan *vs* LV5FU2-Cisplatin**
	QLQ-C30 Scores :	P	P	Mean differences	Mean differences
Functional scales:	Global health	< 0.001	0.48	+ 2.6	+ 5.8
	Physical	< 0.0001	0.18	+ 2.1	+ 9.5
	Role	< 0.001	0.24	+ 3.2	+ 9.1
	Emotional	< 0.001	0.18	+ 2.2	+ 9.4
	Cognitive	< 0.0001	0.33	+ 5.9	+ 8.2
	Social	< 0.01	0.43	+ 3.6	+ 7.3
Symptom scales:	Fatigue	< 0.001	0.26	- 6.2	- 7.4
	Nausea	< 0.0001	0.16	- 1.2	- 10.2
	Pain	< 0.001	0.27	- 0.3	- 8.0
	Dyspnoea	< 0.0001	0.83	- 1.7	- 3.4
	Insomnia	< 0.001	0.19	- 4.0	- 10.4
	Appetite loss	< 0.05	0.18	- 5.6	- 10.9
	Constipation	< 0.0001	0.33	- 7.9	- 7.1
	Diarrhoea	< 0.0001	0.06	- 2.6	- 12.5
	Financial	< 0.0001	0.18	+ 1.3	- 9.1

*Results of the longitudinal QLQ-C30 analysis using a mixed model analysis of variance for repeated measurement (Baseline and the first three follow-ups). Significant if p < 0.05. * Global linear change during the first three follow-ups. Scores vary from 0 (worse) to 100 (best) for functional and global health scale and from 0 (best) to 100 (worse) for symptoms scales.*

Résultats du modèle mixte d'analyse de variance pour mesures répétées (inclusion et 3 premiers suivis). Significatif si p < 0.05. * Variation linéaire globale du score durant les suivis.

Les scores du QLQ-C30 varient de 0 (pire) à 100 (meilleure) pour les dimensions fonctionnelles et de santé globale ; de 100 (pire) à 0 (meilleure) pour les dimensions symptomatiques.

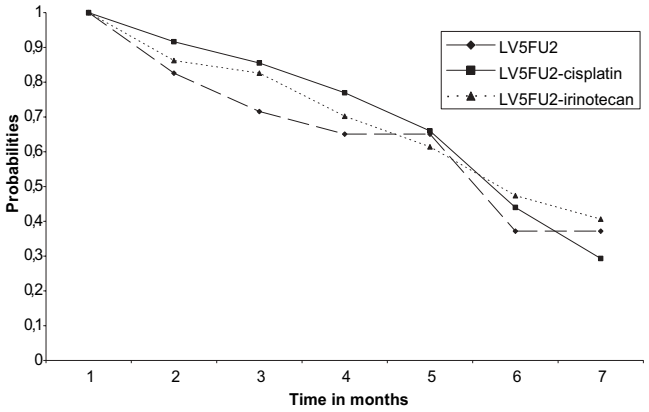

Fig. 3 – Time until definitive Global health score deterioration (Kaplan Meier estimate).

Temps jusqu'à détérioration définitive du score de santé globale (Estimation de Kaplan Meier).

Discussion

From the patient's point of view, QoL results highlight the best toxicity/efficacy ratio in the LV5FU2-Irinotecan based-therapy regimen. As compared to LV5FU2, the best overall response rate, the longest survival did not adversely affect QoL in the irinotecan regimen but did more in the cisplatin arm [7]. While survival until definitive global health deterioration was globally similar between arms, the longitudinal analyses showed that irinotecan-based-therapy presented 14 to 15 scores with a better QoL level. The relative impact of treatment-related toxicity and progressive metastatic disease are difficult to separate [22]. However, our results suggest that irinotecan was the best compromise between clinical efficacy and toxicity. If gastrointestinal and haematological toxicities were more frequent and correlated to global health in the irinotecan regimen, the better efficacy seemed to positively counterbalance their impacts about perceived diarrhoea, fatigue and therefore global health [7]. To preserve functional ability and to improve QoL until progression or death, specific supportive care and prophylactic treatments should be planned to reduce toxicity impact in future palliative trials using irinotecan. The most important subsets of QoL like diarrhoea, fatigue or pain should be specifically assessed and improved in the future phase III trial. If these data complement safety and efficacy from the patient's point of view, we recognize that in a phase II setting, it is difficult to state definitive conclusions regarding the effect of chemotherapy on QoL [22]. The differential treatment impacts could have changed the relative importance of domains constituting their perceived global QoL; this "Response shift" component could have biased the QoL results [32]. The fact that some of the observed differences or correlations in this study did not reach statistical significance may also be due to sample size limitations.

If this study supported the interest of assessing and using QoL in phase II trials, the completion rate limited its feasibility. In palliative settings, many studies have already reported a similar problem regarding failure of completion [20]. In assessable patients, chemotherapies appeared to preserve QoL in the 6-month follow-up. This finding is consistent with the QoL benefits reported with the ELF regimen [38] but differs from the maintained without improvement global QoL found with the ECF regimen [39, 40]. The missing data could explain these differences. The main causes for drop-outs were tumor progression: some patients were still alive but have not submitted assessment or have been assessed without QoL completion [29, 41]. These non-random missing data could have biased the differential treatment impact on QoL [29]: the QoL level was overestimated and more specifically related to the progression-free period and healthy patients [11, 31, 41]. We restrained analyses until the 3rd follow-up in order to reduce these biases. The poorest score imputation was performed to test the robustness of our results in a pessimistic point of view [31]. These conservative estimates are not optimal: the QoL score variability has been reduced and the lacks of information after treatment discontinuation are not resolved [37]. The use of pattern mixture models or sub-group analyses would have been alternatives but were not relevant with few patients [29, 41]. In future trials, FFCD should introduce specific procedures to improve QoL data completion [11, 42, 22]. Protocols should clearly state that QoL completion is required independently of patient health status. The need for help in completing questionnaires should be proposed. Furthermore use of an interview should be feasible in phase II study to ensure compliance [43, 44]. It would be useful and more efficient to reduce the number of assessments during treatment. Their choices should be planned in a clinical meaningful time frame [45].

Firstly, we have reported the rate of patients presenting a stable or improved Global health between baseline and the 3rd follow-up. Reporting these percentage changes from baseline gives the results in clinically relevant terms [46]. Furthermore, it would offer QoL hypothesis in order to design another phase II or phase III trial [22]. However, this presentation is biased by the fact that only patients responding at these two time points contribute data to the analysis and QoL level was not investigated [31, 46]. Secondly we have performed a mixed model analysis of variance; results have been summarized in terms of number of scales for which the mean of Irinotecan-regimen QoL is better than in the other treatments. These presentations could help to globally judge the best impact during follow-up and were retained to complement the main clinical results [7]. Due to missing data and the lack of statistical power, it was difficult to interpret the clinical meaning of these estimated mean differences and longitudinal changes [30, 41]. However, these informative results about QoL level seem consistent with the percentage changes from baseline analyses. The last analysis performed was an estimate of the time until the first observation of Global health score deterioration without any return to a better state during the study. This definition could be used stating that most of the missing data after an observed deterioration is assumed to be related to a continuous deterioration of QoL. This assumption is supported by the design and the drop-out mechanism. While differential QoL level is not explored, this presentation dealing with phase II design could clearly help to estimate the QoL process in a timing point of view and to formulate an hypothesis for future trials. A multiple event survival analysis should be tested in a future study to jointly study progression, death and QoL deterioration.

According to our study and binding phase II designs, we are convinced that these QoL analyses would be relevant to complement the benefit-risk judgement from the patient's point of view. Furthermore, they would be useful to generate hypotheses and to improve logistics [21, 22]. As an example, the new validated gastric cancer module EORTC STO 22 should be warranted in the future phase III trial to increase responsiveness to change and QoL data collection should be optimized [47]. FFCD plans to include a QoL endpoint in future palliative phase II trials in patients with advanced digestive cancer. The way of analysing and presenting QoL data influences the amount of information [31]: future research should be addressed in order to more accurately describe the standard of reporting and analysing QoL data in a phase II trial.

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