

BMJ Open An explorative study to assess the association between health-related quality of life and the recommended phase II dose in a phase I trial: idarubicin-loaded beads for chemoembolisation of hepatocellular carcinoma

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ABSTRACT

Objectives: The objective of this study was to explore the association between health-related quality of life (HRQoL) and the recommended phase 2 dose in a phase I clinical trial according to the Time to HRQoL deterioration approach (TTD).

Setting: This is a phase I dose-escalation trial of transarterial chemoembolisation (TACE) with idarubicin-loaded beads performed in cirrhotic patients with hepatocellular carcinoma. Patients had to complete the EORTC QLQ-C30 HRQoL questionnaire at baseline and at days 15, 30 and 60 after TACE.

Participants: Patients aged ≥ 18 years with HCC unsuitable for curative treatments were evaluated for the study (N=21).

Primary and secondary outcome measurements: The primary objective was to determine the maximum tolerated dose (MTD) of idarubicin loaded after a single TACE session. MTD was defined as the dose level closest to that causing dose-limiting toxicity in 20% of patients. HRQoL was the secondary end point.

Results: Between March 2010 and March 2011, 9, 6 and 6 patients were included at idarubicin dose levels of 5, 10 and 15 mg, respectively. Calculated MTD of idarubicin was 10 mg. At the 10 mg idarubicin dose, patients presented a longer TTD than at 5 mg, for global health status (HR=0.91 (95% CI 0.18 to 4.72)), physical functioning (HR=0.38 (0.04 to 3.22)), fatigue (HR=0.67 (0.18 to 2.56)) and pain (HR=0.47 (0.05 to 4.24)).

Conclusions: These HRQoL results were consistent with the estimated MTD, with a median TTD for global health status of 41 days (21 to NA) at 5 mg, 23 days (20 to NA) at 10 mg and 25 days (17 to NA) at 15 mg. These results show the importance of studying HRQoL in phase I trials.

Trial registration number: NCT01040559; Post-results.

Strengths and limitations of this study

- This study is the first to explore the association between health-related quality of life and the recommended phase II dose in a phase I clinical trial according to the time to deterioration approach.
- Health-related quality of life was longitudinally assessed using the cancer-specific EORTC QLQ-C30 questionnaire during treatment.
- A high completion rate was observed at baseline and at each follow-up.
- Health-related quality of life analysis was performed for exploratory purposes as a secondary end point to this phase I clinical trial, and thus poor precision in the estimations was observed.

BACKGROUND

Hepatocellular carcinoma (HCC) is the fifth most frequent cancer, and the third most common cause of cancer-related death in the world,¹ with most patients cared for in the palliative setting. In palliative care, one of the standard treatments is transarterial chemoembolisation² (TACE), but the prognosis of these patients remains poor. Owing to the condition of these patients in the terminal phase of disease, health-related quality of life (HRQoL) is considered as a valuable end point that is as important as overall survival, in order to investigate the clinical benefit for patients,^{3–5} and is critical when the likelihood of a cure is low, as in

advanced HCC. However, to date, few studies have assessed HRQoL in patients undergoing TACE.

Protocols for TACE implementation vary widely between centres and radiologists, and idarubicin has been shown to be the most cytotoxic drug.⁶ In this context, a recent phase I clinical trial evaluated the safety and efficacy of TACE with idarubicin-loaded beads for the treatment of unresectable HCC.⁷ The primary end point was to determine the maximum tolerated dose (MTD) of idarubicin loaded in drug-eluting beads after a single TACE session. The MTD obtained was 10 mg, defined as the dose level closest to that causing dose-limiting toxicity (DLT) in 20% of patients. The DLT was determined according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) V.3.0,⁸ targeting grades 3/4, as the types of toxicities that could be associated with treatment failure.

The duration of toxicity and/or the occurrence of late toxicity are not taken into account in the definition of DLT. Some moderate toxicities observed over a long period could impair patients' HRQoL, this is the case for the new biological agent assessed in oncology⁹ and could be the case for idarubicin as well. These moderate toxicities are also not taken into account in the usual definition of DLT based on the NCI-CTCAE assessed by clinicians at cycle 1.¹⁰ Therefore, the usual definition of DLT may not appropriately reflect the patient's feelings regarding the tolerability of the treatment received, resulting in overestimation or underestimation of these toxicities.^{11 12} As a result, the dose actually selected for future development may not be the best recommended phase II dose (RP2D).

In this context, the added value of HRQoL as a complement to the usual NCI-CTCAE scale to detect intolerable treatments and doses deserves to be investigated. The added value of HRQoL or other patient-reported outcomes to assess the safety of treatment toxicities has frequently been investigated in the last decade but, to date, it has been poorly investigated in oncology phase I clinical trials, and never in HCC to the best of our knowledge. In many phase I studies, analyses are more descriptive than longitudinal, and HRQoL results are not used to complement interpretation of results, nor to select the RP2D.¹³ One recent study analysed longitudinal HRQoL in a phase I clinical trial, but only compared two time points, namely, before and after treatment.¹⁴ Time to HRQoL score deterioration (TTD)^{15–17} could be an alternative way to analyse these data in a clinically meaningful way.

The objective of this study was to explore the association between HRQoL and RP2D in a phase I trial in patients with HCC. The TTD approach was used, with several definitions of composite end points, both including and not including the occurrence of severe toxicity (grade 3/4 according to the NCI-CTCAE criteria) as assessed by the clinician.

METHODS

Study objectives

Data from a phase I, monocentric, open-label, dose-escalation study of TACE with idarubicin-loaded beads were used. All patients were fully informed of the study and provided signed written informed consent. The protocol was approved by the Ethics Committee, and written approval from the French national health products safety agency ('Agence Française de Sécurité Sanitaire des Produits de Santé') was obtained before the start of the study. The study was registered on ClinicalTrials.gov (identifier: NCT01040559). The design and results of this study have been extensively described elsewhere.⁷

The primary objective was to determine the MTD of idarubicin loaded after a single TACE session. HRQoL was the secondary end point.

Study population and design

Patients aged ≥ 18 years with HCC unsuitable for curative treatments were evaluated for the study. Eligibility criteria were: a confirmed diagnosis of HCC according to criteria from the European Association for the Study of the Liver,¹⁸ Child-Pugh liver function of A to B7 with neither ascites nor jaundice, and Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0–1.

Treatment consisted of a single TACE session with injection of 2 mL drug-eluting beads (DEBs) (DC Bead 300–500 μm , Biocompatibles, Surrey, UK) loaded with idarubicin (Zavedos, Pfizer, Paris, France) at one of the five following escalating doses: 5, 10, 15, 20 or 25 mg. The starting dose level of idarubicin was 10 mg. Idarubicin dose escalation followed a likelihood approach continual reassessment method (CRM).^{19 20}

DLT was defined as any unacceptable toxicity that was possibly, probably, or definitely attributed to treatment. Unacceptable toxicity was defined as any grade 4–5 adverse event from the following categories: allergy/immunology, blood/bone marrow (for neutrophil and platelet count, a grade 4 adverse event was not considered a DLT if it was reversible within 7 days), cardiac arrhythmia, general cardiac, coagulation, constitutional symptoms, gastrointestinal, haemorrhage/bleeding, infection, metabolic/laboratory (except for total bilirubin defined as DLT if >5 times the upper limit of normal for five consecutive days and for creatine defined as a DLT if grade ≥ 3 adverse event), musculo-skeletal/soft tissue, ocular/visual, pain. For other categories of the NCI-CTCAE v3.0, any grade ≥ 3 adverse event defined an unacceptable toxicity.

The MTD was defined as the dose level closest to that causing DLT in 20% of patients within the month after TACE. MTD was also the RP2D.

Cohorts of one patient were sequentially enrolled at one dose level on the basis of the DLT observed within the month after TACE of the previous patient. According to the CRM method, each new patient included was allocated to the dose level for which the

probability of toxicity was the closest to the achievable dose level, that is, the current estimate of the MTD.

HRQoL assessment

HRQoL was evaluated at baseline and at days 15, 30 and 60 after TACE, using the European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30 cancer-specific questionnaire.²¹ The 30-item QLQ-C30 measures five functional scales (physical, role, emotional, cognitive and social functioning), global health status (GHS), financial difficulties and eight symptom scales (fatigue, nausea and vomiting, pain, dyspnoea, insomnia, appetite loss, constipation and diarrhoea).²¹ HRQoL scores were generated according to the EORTC Scoring Manual.²² These scores vary from 0 (worst) to 100 (best) for the GHS and functional scales, and from 0 (best) to 100 (worst) for symptomatic scales. Patients completed the questionnaire fully and without assistance, and were given adequate time to complete this task.

Statistical analysis

Population and statistical considerations

Patients with at least one baseline HRQoL score available were included in the HRQoL analysis (modified intention-to-treat analysis). Prespecified targeted HRQoL dimensions were GHS, physical functioning, fatigue and pain.

Since this was a phase I clinical trial, HRQoL was evaluated for exploratory purposes as a secondary end point. Therefore, no *p* values are provided, while effect size is presented as HR with 95% CI. A five-point difference in HRQoL scores was considered as the minimal clinically important difference (MCID).²³

Descriptive analysis and missing data

Baseline clinical and sociodemographic characteristics are described as median and range for continuous variables, and number and percentage for qualitative variables.

Patients with missing baseline HRQoL questionnaires were described according to idarubicin dose level and time to last follow-up, in order to identify the missing data profile.

Longitudinal analysis

The objective was to explore the association between HRQoL and RP2D using the TTD approach. Thus, the idarubicin level doses were compared according to the TTD approach. Four definitions of TTD were investigated (see online supplementary table A1 in additional file 1):

1. The time from inclusion in the study to a first deterioration with a 5-point MCID as compared to the baseline score;¹⁷
2. Then integrating all-cause death as event (corresponding to HRQoL deterioration-free survival (QFS)).¹⁵

3. The TTD in at least one HRQoL score among the four targeted HRQoL dimensions;¹⁶
4. Then integrating the occurrence of at least one grade 3/4 toxicity according to the NCI-CTCAE criteria. This last definition makes it possible to include toxicity defined according to the NCI-CTCAE scale in the TTD definition.

For each composite definition, the event retained was the first event observed.

Patients with no follow-up score were censored 1 day after baseline and considered as events thereafter (sensitivity analysis).

TTD curves were estimated using the Kaplan-Meier method and described using median with 95% CI. Univariate HR with 95% CI for 10 vs 5 mg idarubicin dose level and univariate HR of 15 mg vs 5 mg idarubicin dose level were estimated using Cox models.

A longer TTD observed at the estimated RP2D, as compared to other doses, for all TTD definitions explored, would indicate that, from a patient's point of view, the RP2D could represent the optimal dose. Conversely, a longer TTD observed at a higher or lower dose than the RP2D for all TTD definitions explored could suggest that the RP2D should be adjusted to a higher or a lower level, respectively.

Univariate Cox regression analyses were conducted as exploratory analyses to investigate factors potentially influencing the last two definitions of TTD, namely:

- ▶ TTD in at least one HRQoL score;
- ▶ TTD in at least one HRQoL score or occurrence of at least one grade 3/4 toxicity.

Variables tested were gender (women vs men), age (continuous variable), PS (1 vs 0), Child-Pugh class (A6 vs A5; B7 vs A5), Cancer of the Liver Italian Program (CLIP) score (2 vs 0; 1 vs 0),^{24 25} the Barcelona Clinic Liver Cancer (BCLC) stage²⁶ (B vs A; C vs A) and the occurrence of DLT (yes vs no). Regarding the definition of TTD in at least one HRQoL score, the time to grade 3/4 toxicity was also tested (as a time dependent variable) in order to investigate the impact of the occurrence of grade 3/4 toxicity on HRQoL. The proportionality of risks hypothesis was checked using the Schoenfeld residuals test.²⁷

All analyses were performed using R software (R development Core Team. R: A Language and Environment for Statistical Computing. R Foundation for Statistical Computing, Vienna, Austria. ISBN 3-900051-07-0, <http://www.R-project.org/> 2010. <http://www.R-project.org/>).

RESULTS

Study population

From March 2010 to March 2012, 21 patients were included: 9, 6 and 6 patients were treated at idarubicin dose levels of 5, 10 and 15 mg, respectively (figure 1). The median age was 64 years (range 45–79) and 18 patients were men (86%). Eighteen patients had good ECOG PS

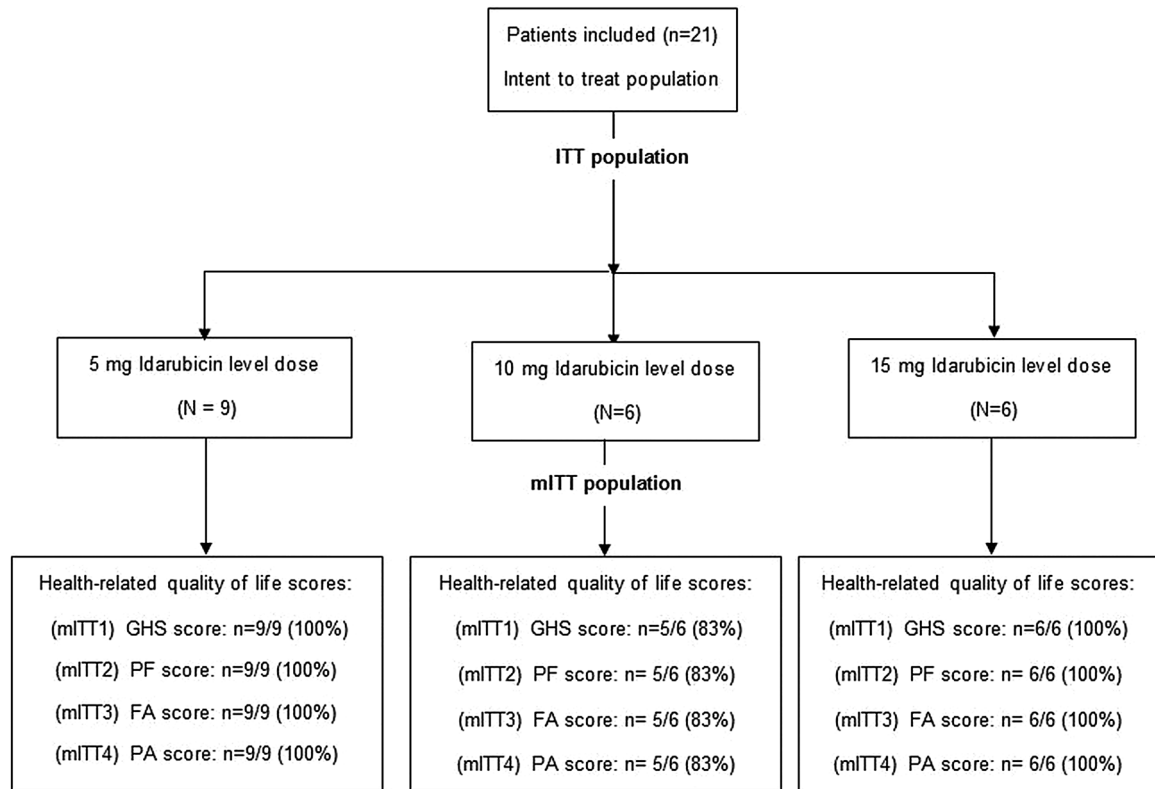


Figure 1 Consort diagram. ITT: intent to treat; mITT: modified intent to treat (ie, patients with at least the baseline HRQoL score); GHS, Global Health Status; PF, physical functioning; FA, fatigue; PA: pain.

(86%). The baseline characteristics of the patients are summarised in [table 1](#). DLT was observed for three patients, and the estimated MTD of idarubicin was 10 mg.⁷

Twenty patients (95%) completed the baseline HRQoL questionnaire: 18 patients (86%) at day 15 (median time of 19 days (range 14–23)); 21 patients (100%) at day 30 (median time of 35 days (range 29–43)) and 17 patients (81%) at day 60 (median time of 70 days (range 64–92)) after TACE. The patient who did not complete the baseline HRQoL questionnaire was included at the 10 mg dose level, and subsequently completed all follow-up questionnaires.

Longitudinal analysis

[Table 2](#) displays the results of the TTD and QFS analyses according to idarubicin level dose for the four-targeted dimensions of HRQoL with the sensitivity analysis.

TTD with a 5-point MCID of GHS

Eleven patients (55%) presented a significant deterioration of the GHS with a 5-point MCID among the 20 included patients in the longitudinal analysis ([figure 2A](#)): the median TTD was 41 days (21 to not available (NA)) at 5 mg, 23 days (20 to NA) at 10 mg and 25 days (17 to NA) at 15 mg. The HR for 10 vs 5 mg was 0.91 (0.18 to 4.72). The HR for 15 vs 5 mg was 1.60 (0.43 to 5.98) ([table 2](#)).

Among the 20 included patients, 14 (70%) presented with significant deterioration of the GHS or death (all

causes): the median QFS was 41 days (21 to NA) at 5 mg, 140 days (20 to NA) at 10 mg and 25 days (17 to NA) at 15 mg. The HR for 10 vs 5 mg was 1.35 (0.32 to 5.66) and 1.82 (0.47 to 6.96) for 15 vs 5 mg ([table 2](#)).

TTD with a 5-point MCID of physical functioning

Ten patients (50%) presented a significant deterioration of physical functioning with a 5-point MCID ([figure 2B](#)): the median TTD was 42 days (21 to NA) for 5 mg, not available (23 to NA) for 10 mg and 61 days (14 to NA) for 15 mg. The HR for 10 vs 5 mg was 0.38 (0.04 to 3.22), and 1.07 (0.26 to 4.50) for 15 vs 5 mg ([table 2](#)).

Integrating all-cause deaths as an event, 14 patients (70%) presented a significant deterioration of physical functioning with a 5-point MCID or death: the median QFS was 42 days (21 to NA) for 5 mg, 257 days (23 to NA) for 10 mg and 61 days (14 to NA) for 15 mg. The HR for 10 vs 5 mg was 0.44 (0.09 to 2.14), and 1.51 (0.41 to 5.59) for 15 vs 5 mg ([table 2](#)).

TTD with a 5-point MCID of fatigue

Sixteen patients (80%) presented a significant increase in fatigue with a 5-point MCID ([figure 2C](#)): the median TTD was 21 days (19 to NA) for 5 mg, 29 days (20 to NA) for 10 mg and 19 days (14 to NA) for 15 mg. The HR for 10 vs 5 mg was 0.67 (0.18 to 2.56), and 1.04 (0.31 to 3.49) for 15 vs 5 mg ([table 2](#)). The same results were observed for QFS of fatigue.

Table 1 Baseline characteristics for all patients and according to idarubicin dose (N=21)

Characteristic	All patients N (%)	5 mg (N=9) N (%)	10 mg (N=6) N (%)	15 mg (N=6) N (%)
Age, median (range)	64 (45–79)	64 (45–79)	65 (52–74)	69 (51–79)
Gender				
Female	3 (14)	1 (11)	0 (0)	2 (33)
Male	18 (86)	8 (89)	6 (100)	4 (67)
Child-Pugh class				
A5	10 (48)	3 (33)	4 (67)	3 (50)
A6	6 (28)	2 (22)	2 (33)	2 (33)
B7	5 (24)	4 (45)	0 (0)	1 (17)
BCLC stage				
A	5 (24)	0 (0)	1 (17)	4 (67)
B	15 (71)	9 (100)	4 (66)	2 (33)
C	1 (5)	0 (0)	1 (17)	0 (0)
CLIP score				
0	5 (24)	1 (11)	2 (33)	2 (33)
1	8 (38)	4 (44)	2 (33)	2 (33)
2	7 (33)	4 (44)	2 (33)	1 (17)
Missing	1 (5)	0 (0)	0 (0)	1 (17)
Performance status				
0	18 (86)	8 (89)	5 (83)	5 (83)
1	3 (14)	1 (11)	1 (17)	1 (17)
Number of nodules, median (range)	2 (1–6)	2 (1–4)	4 (1–6)	2 (1–4)

BCLC, Barcelona Clinic Liver Cancer; CLIP, Cancer of the Liver Italian Program.

TTD with a 5-point MCID of pain

Eleven patients (55%) presented a significant increase in pain level with a 5-point MCID (figure 2D): the median TTD was 76 days (21 to NA) for 5 mg, not available (23 to NA) for 10 mg and 27 days (14 to NA) for 15 mg. The HR for 10 vs 5 mg was 0.47 (0.05 to 4.24), and 2.25 (0.55 to 9.14) for 15 vs 5 mg (table 2).

Integrating all-cause death as an event, 14 patients (70%) presented a significant pain deterioration with a 5-point MCID or death: the median QFS was 76 days (21 to NA) for 5 mg, 257 days (23 to NA) for 10 mg and 26 days (14 to NA) for 15 mg, respectively. The HR for 10 vs 5 mg was 0.37 (0.08 to 1.87), and 2.15 (0.55 to 8.39) for 15 vs 5 mg (table 2).

TTD in at least one HRQoL score, with or without toxicity as an event

Table 3 contains the results of the TTD in at least one HRQoL score, including toxicity or not, as an event with the sensitivity analysis.

Eighteen patients (90%) presented a significant deterioration of at least one HRQoL score with a 5-point MCID: the median TTD was 31 days (19 to NA) for 5 mg, 29 days (20 to NA) for 10 mg and 17 days (14 to NA) for 15 mg. The HR for 10 vs 5 mg was 0.83 (0.22 to 3.17), and 4.47 (1.33 to 15.09) for 15 vs 5 mg (table 3).

Eighteen of 20 patients (90%) presented a significant deterioration of at least one HRQoL score with a 5-point MCID or a grade 3/4 toxicity: the median TTD was 31 days (19 to NA) for 5 mg, 8 days (5 to NA) for 10 mg and 6 days (1 to NA) for 15 mg. The HR for 10 vs 5 mg

was 0.96 (0.52 to 3.66), and 3.31 (1.04 to 10.46) for 15 vs 5 mg (table 3).

Univariate Cox Analyses for TTD of at least one HRQoL score including toxicity or not as an event

Table 4 presents the results of the univariate Cox analyses for the TTD in at least one score with or without grade 3/4 toxicity as an event and sensitivity analysis integrating no follow-up as an event.

Women presented a shorter TTD in at least one HRQoL score than men did (HR=4.39 (1.11 to 17.36)). The time to grade 3/4 toxicity was also associated with a shorter TTD, whether integrating no follow-up as an event or not, and the value 1 was not included in the 95% CI (HR=3.84 (1.31 to 11.28) and HR=4.39 (1.41 to 13.68), respectively). Surprisingly, the occurrence of DLT seemed to be associated with a longer TTD in at least one HRQoL score, integrating no follow-up as an event or not, but with a 95% CI including 1 (HR=0.67 (0.15 to 2.96) and HR=0.72 (0.16 to 3.17), respectively).

DISCUSSION

The objective of this study was to explore the association between HRQoL and the RP2D in a phase I clinical trial of HCC with the time to deterioration approach.

Patients at the 10 mg idarubicin dose level tended to present a longer time to GHS, physical functioning, fatigue and pain deterioration, as compared with patients at the 5 mg idarubicin dose level, except for the sensitivity analysis of GHS, for which a HR (10 vs 5 mg) >1 was observed.

Table 2 Time to quality of life score deterioration of at least five points as compared to the baseline score, integrating all-cause death as an event (QFS) or not (TTD), with sensitivity analyses considering patients with no baseline score or with no follow-up score as events

	TTD ≥5-point MCID			TTD ≥5-point MCID or no follow-up			QFS ≥5-point MCID			QFS ≥5-point MCID or no follow-up		
	N (events)	Median (95% CI)	HR (95% CI)	N (events)	Median (95% CI)	HR (95% CI)	N (events)	Median (95% CI)	HR (95% CI)	N (events)	Median (95% CI)	HR (95% CI)
<i>Global health status</i>												
All	20 (11)	31 (21 to NA)		20 (12)	30 (21 to NA)		20 (14)	31 (21 to NA)		20 (15)	30 (21 to NA)	
5 mg	9 (5)	41 (21 to NA)	1	9 (5)	41 (21 to NA)	1	9 (7)	41 (21 to NA)	1	9 (7)	41 (21 to NA)	1
10 mg	5 (2)	23 (20 to NA)	0.91 (0.18 to 4.72)	5 (3)	23 (20 to NA)	1.35 (0.32 to 5.65)	5 (3)	140 (20 to NA)	1.35 (0.32 to 5.66)	5 (4)	23 (20 to NA)	1.77 (0.48 to 6.62)
15 mg	6 (4)	25 (17 to NA)	1.60 (0.43 to 5.98)	6 (4)	25 (17 to NA)	1.56 (0.64 to 5.88)	6 (4)	25 (17 to NA)	1.82 (0.47 to 6.96)	6 (4)	25 (17 to NA)	1.75 (0.46 to 6.66)
<i>Physical functioning</i>												
All	20 (10)	92 (29 to NA)		20 (11)	42 (23 to NA)		20 (14)	92 (29 to NA)		20 (15)	42 (23 to NA)	
5 mg	9 (5)	42 (21 to NA)	1	9 (5)	41 (21 to NA)	1	9 (7)	42 (21 to NA)	1	9 (7)	42 (21 to NA)	1
10 mg	5 (1)	NA (23 to NA)	0.38 (0.04 to 3.22)	5 (2)	NA (23 to NA)	0.75 (0.14 to 3.88)	5 (3)	257 (23 to NA)	0.44 (0.09 to 2.14)	5 (4)	257 (23 to NA)	0.67 (0.17 to 2.63)
15 mg	6 (4)	61 (14 to NA)	1.07 (0.26 to 4.50)	6 (4)	61 (14 to NA)	1.05 (0.25 to 4.42)	6 (4)	61 (14 to NA)	1.51 (0.41 to 5.59)	6 (4)	61 (14 to NA)	1.41 (0.39 to 5.09)
<i>Fatigue</i>												
All	20 (16)	21 (19 to 43)		20 (17)	21 (19 to 43)		20 (16)	21 (19 to 43)		20 (17)	21 (19 to 43)	
5 mg	9 (9)	21 (19 to NA)	1	9 (9)	21 (19 to NA)	1	9 (9)	21 (19 to NA)	1	9 (9)	21 (19 to NA)	1
10 mg	5 (3)	29 (20 to NA)	0.67 (0.18 to 2.56)	5 (4)	23 (20 to NA)	0.90 (0.27 to 3.01)	5 (3)	29 (20 to NA)	0.67 (0.18 to 2.56)	5 (4)	23 (20 to NA)	0.90 (0.27 to 3.01)
15 mg	6 (4)	19 (14 to NA)	1.04 (0.31 to 3.49)	6 (4)	19 (14 to NA)	1.02 (0.31 to 3.41)	6 (4)	19 (14 to NA)	1.04 (0.31 to 3.49)	6 (4)	19 (14 to NA)	1.02 (0.31 to 3.41)
<i>Pain</i>												
All	20 (11)	76 (23 to NA)		20 (12)	37 (21 to NA)		20 (14)	76 (23 to NA)		20 (15)	37 (21 to NA)	
5 mg	9 (6)	76 (21 to NA)	1	9 (6)	76 (21 to NA)	1	9 (7)	76 (21 to NA)	1	9 (7)	76 (21 to NA)	1
10 mg	5 (1)	NA (23 to NA)	0.47 (0.05 to 4.24)	5 (2)	NA (23 to NA)	0.94 (0.17 to 5.16)	5 (3)	257 (23 to NA)	0.37 (0.08 to 1.87)	5 (4)	257 (23 to NA)	0.59 (0.15 to 2.36)
15 mg	6 (4)	27 (14 to NA)	2.25 (0.55 to 9.14)	6 (4)	26 (14 to NA)	2.14 (0.53 to 8.69)	6 (4)	26 (14 to NA)	2.15 (0.55 to 8.39)	6 (4)	26 (14 to NA)	1.88 (0.50 to 7.05)

MCID, minimal clinically important difference; QFS, Quality of life score deterioration Free Survival; HRQoL deterioration-free survival; TTD, time to HRQoL score deterioration.

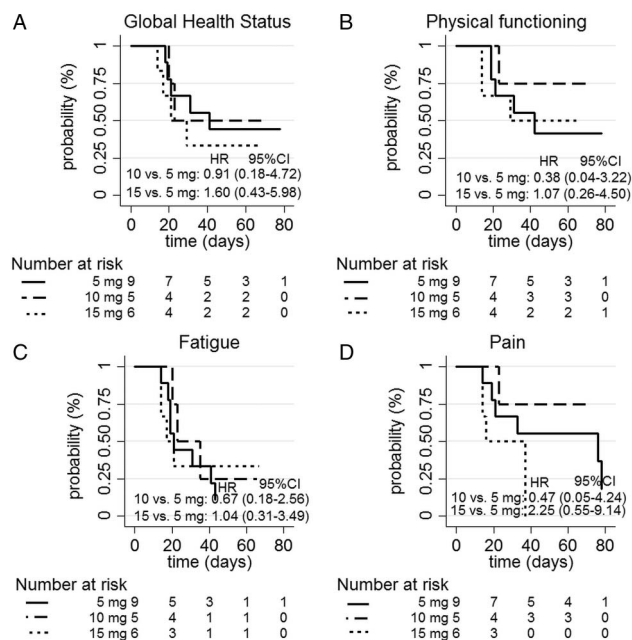


Figure 2 Kaplan-Meier survival curves according to idarubicin dose level for the four-targeted dimensions of the QLQ-C30 regarding the time to Health-related quality of life score deterioration with a 5-point minimal clinically important difference.

Patients included at the 15 mg idarubicin dose level presented a trend towards a shorter time to deterioration in GHS, physical functioning, fatigue and pain, as compared with patients at the 5 mg idarubicin dose level, whatever the definition of deterioration applied, with a HR (15 vs 5 mg) >1.

Regarding the TTD in at least one HRQoL score, whether or not integrating toxicity as an event:

- ▶ Patients included at the 10 mg idarubicin dose level presented a longer TTD than those included at 5 mg, with a HR <1, except for sensitivity analysis integrating no follow-up as an event.

- ▶ Patients included at the 15 mg idarubicin dose level presented a shorter TTD than those included at 5 mg, with a HR >1.

Overall, patients included at the 10 mg idarubicin dose level seemed to have a longer TTD of HRQoL than patients included at the 5 mg or 15 mg idarubicin dose levels. HRQoL results are thus consistent with the 10 mg idarubicin dose level selected as the MTD, whereby patients included at the 10 mg idarubicin dose level presented acceptable toxicities and a trend towards better HRQoL profile than did patients included at either the 5 or 15 mg idarubicin dose levels, although these results were not significant. These results confirm that, from a patient's point of view, 10 mg could represent the optimal dose, and was linked with RP2D.

Moreover, Cox analyses highlighted that the time to grade 3/4 toxicity was associated with a shorter TTD in at least one HRQoL score with a HR >1. Thus, the occurrence of some toxicities during treatment has an impact on HRQoL. This suggests that the assessment of toxicities by the clinician is coherent with the patient's perception of their own HRQoL level. However, the occurrence of DLT seemed to be associated with a shorter TTD in at least one HRQoL score, but with the value of 1 included in the 95% CI. This divergent result could be due to the low number of patients experiencing DLT (only 3 DLT events occurred).

The main limitation of this study is the limited number of patients included, inherent to the study design (phase I clinical trial), and, consequently, poor precision in the estimations. However, this limitation also concerns the other end points, including the occurrence of toxicities. In any case, this study was performed for exploratory purposes only. All trends observed here represent a first indication of the impact of the idarubicin dose level on HRQoL, but the lack of statistical power and precision preclude any definitive conclusions. Another limitation is the limited number of

Table 3 Time to deterioration in at least one health-related quality of life score considering grade 3/4 toxicity as an event or not, with sensitivity analysis considering patients with no follow-up as events

Deterioration in at least one HRQoL score				Deterioration in at least one HRQoL score or grade 3/4 toxicity		
	N (events)	Median days (95% CI)	HR (95% CI)	N (events)	Median days (95% CI)	HR (95% CI)
<i>TTD</i>						
All	20 (18)	21 (19 to 42)		20 (18)	17 (8 to 42)	
5 mg	9 (9)	31 (19 to NA)	1	9 (9)	31 (19 to NA)	1
10 mg	5 (3)	29 (20 to NA)	0.83 (0.22 to 3.17)	5 (3)	8 (5 to NA)	0.96 (0.52 to 3.66)
15 mg	6 (6)	17 (14 to NA)	4.47 (1.33 to 15.09)	6 (6)	6 (1 to NA)	3.31 (1.04 to 10.46)
<i>TTD or no-follow-up</i>						
All	20 (19)	21 (19 to 41)		20 (19)	14 (6 to 41)	
5 mg	9 (9)	31 (19 to NA)	1	9 (9)	31 (19 to NA)	1
10 mg	6 (5)	23 (20 to NA)	1.10 (0.33 to 3.68)	5 (4)	8 (5 to NA)	1.30 (0.39 to 4.34)
15 mg	6 (6)	17 (14 to NA)	3.95 (1.20 to 13.01)	6 (6)	6 (1 to NA)	3.05 (0.98 to 9.46)

HRQoL, health-related quality of life; TTD, time to HRQoL score deterioration.

Table 4 Univariate Cox analyses for time to deterioration in at least one score with or without grade 3/4 toxicity as an event, and sensitivity analysis integrating no follow-up as an event

	MCID \geq 5 points		MCID \geq 5 points or no follow-up	
	N (events)	HR (95% CI)	N (events)	HR (95% CI)
<i>TTD in at least one score</i>				
Gender				
men	20 (18)	1	20 (19)	1
women		4.39 (1.11 to 17.36)		3.60 (0.93 to 13.88)
Age*	20 (18)	0.96 (0.90 to 1.02)	20 (19)	0.96 (0.90 to 1.02)
Performance status				
0	20 (18)	1	20 (19)	1
1		2.02 (0.53 to 7.63)		1.80 (0.49 to 6.67)
Child-Pugh class				
A5	20 (18)	1	20 (19)	1
A6		3.69 (1.07 to 12.72)		2.97 (0.90 to 9.79)
B7		2.22 (0.67 to 7.32)		1.86 (0.59 to 5.92)
Score CLIP				
0	19 (17)	1	19 (18)	1
1		1.26 (0.32 to 4.90)		0.95 (0.28 to 3.27)
2		1.56 (0.38 to 6.37)		1.17 (0.32 to 4.22)
BCLC stage				
A	20 (18)	1	20 (19)	1
B		0.53 (0.17 to 1.62)		0.59 (0.20 to 1.80)
C		0.80 (0.09 to 6.99)		0.81 (0.09 to 7.05)
Idarubicin level dose, mg				
5	20 (18)	1	20 (19)	1
10		0.83 (0.22 to 3.17)		1.10 (0.33 to 3.68)
15		4.47 (1.33 to 15.09)		3.95 (1.20 to 13.01)
DLT occurrence				
No	20 (18)	1	20 (19)	1
Yes		0.72 (0.16 to 3.17)		0.67 (0.15 to 2.96)
Time to toxicity*	20 (18)	4.39 (1.41 to 13.68)	20 (19)	3.84 (1.31 to 11.28)
<i>TTD in at least one score or toxicity of grade 3/4</i>				
Gender				
Men	20 (18)	1	20 (19)	1
Women		3.18 (0.85 to 11.86)		2.81 (0.76 to 10.3)
Age*	20 (18)	0.98 (0.93 to 1.03)	20 (19)	0.97 (0.92 to 1.03)
Performance status				
0	20 (18)	1	20 (19)	1
1		1.55 (0.42 to 5.76)		1.39 (0.38 to 5.09)
Child-Pugh class				
A5	20 (18)	1	20 (19)	1
A6		3.82 (1.04 to 14.01)		2.98 (0.86 to 10.34)
B7		1.89 (0.57 to 6.23)		1.59 (0.50 to 5.05)
Score CLIP				
0	19 (17)	1	19 (18)	1
1		1.20 (0.35 to 4.11)		0.94 (0.30 to 2.98)
2		1.49 (0.40 to 5.51)		1.15 (0.34 to 3.92)
BCLC stage				
A	20 (18)	1	20 (19)	1
B		0.34 (0.11 to 1.08)		0.40 (0.13 to 1.22)
C		1.10 (0.12 to 9.84)		1.06 (0.12 to 9.35)
Idarubicin level dose, mg				
5	20 (18)	1	20 (19)	1
10		0.96 (0.25 to 3.66)		1.30 (0.39 to 4.34)
15		3.31 (1.04 to 10.46)		3.05 (0.98 to 9.46)
DLT occurrence				
No	20 (18)	1	20 (19)	1
Yes		1.05 (0.29 to 3.81)		0.98 (0.27 to 3.54)

*Time dependent variable.

†Continuous variable.

BCLC, Barcelona Clinic Liver Cancer; CLIP, Cancer of the Liver Italian Program; DLT, dose-limiting toxicity; MCID, minimal clinically important difference; TTD, time to HRQoL score deterioration.

measurement times (only four measures), which could also explain the low number of events observed for TTD, and the unavailability of median TTD. In future phase I clinical trials, more measurement times should be added in order to better capture longitudinal trends in HRQoL. Variability in the measurement time was also observed, due to logistical constraints in some hospitals in performing TACE.

Several definitions of TTD were explored, of which some included toxicity as an event, and some did not. For the composite definition, the treatment effect should be the same on each component in order to be valid (deterioration of HRQoL and toxicity).

Our results suggest that HRQoL data complement previous results obtained on toxicity, as assessed by the NCI-CTCAE scale, and consolidate the selection of the RP2D. Thus, the added value of HRQoL in phase I clinical trials could be also considered, since it may help to improve the accuracy and definition of the RP2D for future development. Of course, the objective of future phase I clinical trials should not be to optimise TTD instead of finding the highest dose with acceptable toxicity. Rather, the aim should be to complement classical dose-finding analysis with additional HRQoL analysis, in order to determine whether the analysis of HRQoL can help to confirm the RP2D, or to capture potentially unlisted effects.

The RP2D is classically based on the occurrence of limiting grade 3/4 toxicities according to the NCI-CTCAE scale. This scale was initially developed for cytotoxic chemotherapies administered in a limited number of chemotherapy cycles including rest periods. Molecular targeted agents are generally given over long periods with continuous schedules. Moderate toxic side effects persisting over a long period have been shown to be frequent, and are not considered as DLT events, even if they affect the patient's daily life.¹⁰ Moreover, the assessment made by clinicians generally results in underestimation or overestimation of patients' side effects.²⁸ In this way, patient self-reported assessment of toxicity could be considered to be more accurate than the clinician's assessment.²⁹ In this regard, a patient-reported outcomes version of the common terminology criteria for adverse events (PRO-CTCAE) was recently developed by the National Cancer Institute.^{30 31} Although this new scale allows patient self-assessment of toxicity, it nevertheless will not solve the issue of moderate toxic side effects persisting over a long-period, which can have an impact on patients' HRQoL. In this context, HRQoL assessment, as well as other patient-reported symptoms, could be very helpful in a phase I clinical trial to take into account the patient's perception of the tolerability of the treatment received.⁹ In this study, HRQoL was assessed up to 2 months after TACE, while DLT was defined based on toxicities observed up to 1 month after TACE. It seems important, in other phase I studies, to take into account treatment side effects and their impact on the patient's HRQoL in the long term, since

molecular targeted agents are expected to be delivered over long periods. It can also help to better preserve HRQoL in phase II clinical trials, if the planned dose is adapted and if supportive care is also provided.

In the TTD approach used to analyse longitudinal HRQoL, the middle dose presented the longest TTD for most of the definitions of deterioration investigated. This method may be appropriate under the assumption of a monotone increasing dose–efficacy relationship and, indeed, this is the assumption behind the main statistical models for longitudinal HRQoL analysis. It is expected that the TTD increases as efficacy increases, and then decreases as toxicity increases. Since we are looking for a balance between toxicity/efficacy, TTD can be a useful way to capture this balance.

To the best of our knowledge, this is the first study to investigate TTD in a HRQoL score in the framework of a phase I oncology clinical trial. Several studies have investigated HRQoL in phase I clinical trials, but results are generally descriptive and poorly exploited regarding the primary objective of the phase I trial.¹³ To the best of our knowledge, no study to date has compared the HRQoL score according to the molecular dose level allocated to the patient, and the occurrence or not of toxicity or DLT. This study represents a first approach to exploring the added value of HRQoL in phase I clinical trials, but research and reflection about the assessment of HRQoL or other patient-reported outcomes in phase I clinical trials need to be refined.

The QLQ-C30 questionnaire used in this study may not be the most appropriate HRQoL tool for patients included in a phase I trial. The development of a specific HRQoL questionnaire—more focused on symptoms—for phase I oncology trials could thus be necessary in order to capture all the relevant information regarding this specific category of patients.

CONCLUSIONS

To conclude, this study highlights that patients with HCC undergoing TACE at the 10 mg idarubicin dose level, corresponding to the MTD, mainly presented a trend towards longer TTD than patients included at the 5 or 15 mg doses, regardless of the definition of deterioration applied, although the differences were not significant. This study suggests the added value of patient-reported symptoms and HRQoL of patients as a complement to the usual toxicity assessment and DLT definition. Finally, an improvement in patient HRQoL could encourage better compliance with treatment.³²

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