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Effectiveness assessment of riluzole in the prevention of oxaliplatin-induced peripheral neuropathy: RILUZOX-01: protocol of a randomised, parallel, controlled, double-blind and multicentre study by the UNICANCER-AFSOS Supportive Care intergroup

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ABSTRACT

Introduction Most patients (>70%) experience acute neuropathic symptoms shortly after oxaliplatin infusions. These symptoms are not always resolved between infusions. Overall, 30%–50% of patients suffer from chronic oxaliplatin-induced peripheral neuropathy (OIPN). This cumulative and dose-dependent sensory neuropathy limits compliance or results in oxaliplatin-based chemotherapies to be substituted with less neurotoxic agents. These treatment changes impair clinical outcomes, and may be associated with comorbidities, such as distress, depression and anxiety. Currently, no drug used to prevent or treat OIPN is sufficiently effective to be used routinely in clinical practice. There is, thus, an unmet therapeutic need to reduce the intensity of and/or prevent OIPN. We hypothesised that riluzole would be an excellent candidate to address this public health issue. Riluzole is approved for treating amyotrophic lateral sclerosis. In animals, there is a beneficial effect on sensorimotor and pain disorders, as well as related comorbidities, after repeated administration of oxaliplatin. In humans, riluzole has shown neuroprotective, anxiolytic and antidepressive effects.

Methods and analysis RILUZOX-01 trial was designed as a randomised, controlled, double-blind study to evaluate the efficacy of riluzole to prevent OIPN. Patients with colorectal cancer and initiating adjuvant oxaliplatin-based chemotherapy are eligible. Patients (n=210) will be randomly assigned to either riluzole or placebo, concomitantly with chemotherapy. The primary endpoint is the change in OIPN intensity, assessed by the sensory scale of the QLQ-CIPN20, after six 2-week cycles of chemotherapy. Secondary endpoints include incidence and severity of neuropathy, grade of sensory neuropathy, intensity and features of neuropathic pain, health-related quality of life, disease-free survival, overall survival and safety.

Strengths and limitations of this study

► First clinical study to assess riluzole to prevent oxaliplatin-induced peripheral neuropathy.
► Randomised, double-blind, controlled study.
► Intention-to-treat analysis.
► Metastatic cancer population not considered.
► Post-chemotherapy follow-up limited to 12 months.

INTRODUCTION

In recent years, the therapeutic management of cancer has evolved with improved patients' survival. However, most anticancer agents induce adverse effects which significantly impact the quality of life of patients and in some cases, cause early discontinuation of treatments that can compromise the effective clinical outcome.[1 2] Consequently, cancer therapy is a delicate balance between minimising adverse effects without compromising the anticancer efficacy. This objective is even more difficult when anticancer agents have neurotoxic effects responsible for disabling sensory and motor disorders. Chemotherapy-induced peripheral neuropathy (CIPN), regarded as a potentially serious

adverse effects, is observed in >70% of patients treated with oxaliplatin.[3] Most of the patients experience sensory polyneuropathy including loss of sensitivity, paraesthesia, dysesthesia, burning sensations and acute pain induced or exacerbated by the cold. These neuropathies are located in the extremities and in the face and occur within hours or days after oxaliplatin infusions (acute neuropathy). These symptoms do not always resolve between treatment cycles,[4] and 30%–50% of patients suffer from chronic oxaliplatin-induced peripheral neuropathy (OIPN).[5] This cumulative and dose-dependent sensory neuropathy[6] leads to dose modifications, treatment delay and drug substitution with less neurotoxic agents. These treatment changes may reduce the effective clinical outcomes[7] and may be accompanied by comorbidities such as distress, depression and anxiety.[8] In addition, the onset and chronic development of CIPN have important economic consequences. Health outcomes, healthcare (ie, medical and drug) and work loss costs incurred by patients with CIPN in four tumour types revealed that healthcare costs were $17 344 higher for patients with CIPN compared with those without.[9] Currently, none of the drugs used for preventing or treating OIPN, except for duloxetine as curative treatment,[10] are sufficiently effective to be used routinely in clinical practice.[11]" Therefore, when severe neuropathy occurs, dose reduction or discontinuation of chemotherapy are the main options to limit CIPN progression.[12 13]

At present, we have a better understanding of the mechanism through which anticancer agents induce neurotoxicity.[14–16] Oxaliplatin is known to damage the nuclei of DRG neurons, and induces channelopathy mainly on voltage-gated sodium channels, but also on potassium channels of the K2P family (TREK, TRAAK).[17 18] Notably, knock-out animals for TREK and TRAAK channels exhibit an exaggerated cold sensitivity similar to that observed in oxaliplatin-treated animals.[19] In addition, oxaliplatin fails to induce cold hypersensitivity in knock-out mice for TREK and TRAAK.[17] We have also demonstrated that oxaliplatin modifies cold-specific fibres excitability by decreasing their expression level, that is, inhibitor potential of K2P channels,[17] which in combination with TRPM8 defined the cold threshold.[19] Cumulatively, these results suggested a key role of TREK and/or TRAAK channels in oxaliplatin-induced neuropathic symptoms. We, therefore, postulated that activating these TREK/TRAAK channels could compensate their reduced expression and re-establish a normal sensory perception. Riluzole, an oral drug used for the treatment of amyotrophic lateral sclerosis (ALS)[20] activates TREK-1 and TRAAK channels,[21] as well as TREK-2, a similar channel also involved in pain perception.[18]

The neuroprotective effect of riluzole
Preclinical studies have shown that riluzole completely suppresses the pain and neuronal damage in post-traumatic neuropathy and cervical radiculopathy models.[22–25] In oxaliplatin-treated animals, riluzole prevents the excessive accumulation of glutamate, as previously observed in ischaemic animals.[26–29] This effect preserves neuronal structures in the brain, spinal cord and retinal ischaemia.[26 27 30] Other studies have demonstrated a neuroprotective role of riluzole in animal models of Parkinson's disease,[31 32] and post-traumatic neuropathic pain.[33] We recently assessed and highlighted the benefit of riluzole for sensorimotor and painful disorders, preventing oxaliplatin-induced peripheral nerve functional and morphological alterations, as well as related oxaliplatin-induced comorbidities.[34]

Riluzole and its interaction with the anticancer effect of oxaliplatin
According to the recent recommendations of the Analgesic, Anaesthetic, and Addiction Clinical Trial Translations, Innovations, Opportunities, and Networks (ACTTION),[35] the study of new treatments related to anticancer chemotherapy must consider their impact on disease progression and/or survival without relapse (time after chemotherapy without cancer progression or tumour recurrence). Several in vitro studies reported that riluzole reduced the migration, invasion and proliferation of cells derived from melanoma,[36] HT-29 (primary colon-derived) and T84 (lung metastasis-derived) human cell lines.[34] In vivo, we have shown in a spontaneous colorectal cancer (CRC) mouse model (APC$^{min/+}$ mice) that riluzole combined with oxaliplatin did not alter the action of oxaliplatin: the rate of decrease in the number of tumours after treatment with oxaliplatin was identical with or without riluzole.[34]

Rationale
Based on robust preclinical data, the use of riluzole could prevent and/or reduce the symptoms of OIPN, as well as limit the incidence of related comorbidities. Moreover, riluzole has proven neuroprotective,[37 38] anxiolytic[39 40] and antidepressive[39 41] effects in several clinical studies. Thus, riluzole may be an excellent candidate to address this public health issue.

No clinical studies have assessed the effect of riluzole on the symptoms of CIPN. However, patients with spinal cord injuries when treated with riluzole improved their neurological status (combining emotional, motor and neuropathic pain), compared with those treated with placebo.[42] Also, riluzole was not associated with significant adverse effects. Furthermore, the neuroprotective role of riluzole has been established in patients with ALS[43 44] and Parkinson's disease.[45] The neuroprotective property of riluzole and its beneficial effect on OIPN-related comorbidities provide a rationale for combining it with oxaliplatin.[46 47] Thus, in this study, we will assess the efficiency of riluzole in reducing the severity and incidence of OIPN. This study could rapidly provide a new therapeutic strategy to limit neurotoxic adverse effects induced by oxaliplatin, with riluzole expected to be well tolerated.[48]
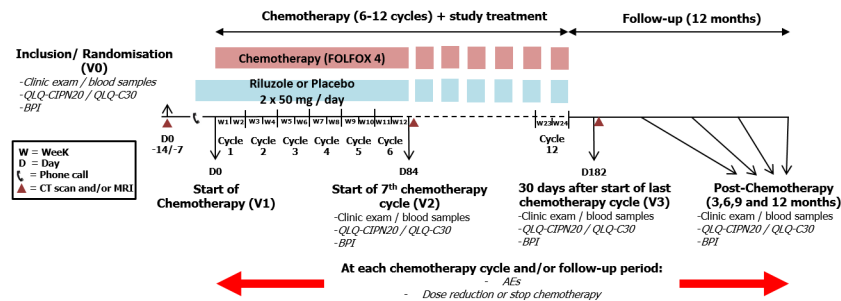
Figure 1 Study design. A phone call is planned to remind the patient to take the study treatment 7 days before starting chemotherapy (V1), only if the inclusion/randomisation visit (V0) takes place more than 7 days before V1. AEs, adverse effects; BPI, brief pain inventory QLQ-CIPN20, quality of life questionnaire-chemotherapy-induced peripheral neuropathy; scan. scanner; V. visit.

METHODS AND ANALYSIS

Our study was designed in accordance with the recent ACTTION recommendations.[35] RILUZOX-01 is a randomised, parallel, controlled, double-blind, multi-centre phase II clinical trial evaluating the preventive efficacy and safety of riluzole for OIPN, in CRC patients initiating oxaliplatin-based chemotherapy (FOLFOX 4). For each patient, the study will last for 16–19 months, comprising 13–25 weeks of treatment (depending on the number of chemotherapy cycles, between 6 and 12 cycles of FOLFOX 4) and 12 months of follow-up. The study design is shown in figure 1. The study plans to enrol 210 patients in 20 sites in France in 24 months.

Study objectives

Our primary objective is to evaluate the preventive efficacy of riluzole on the intensity of OIPN symptoms, in patients with CRC, after six cycles of oxaliplatin-based chemotherapy (FOLFOX 4).

Secondary objectives are as follows:
► To assess the effect of riluzole on
  – Neuropathic pain.
  – Incidence and severity of neuropathy (motor and autonomic).
  – Impact on health-related quality of life (HRQoL).
  – Disease-free survival.
  – Overall survival.
  – Time to treatment failure.
  – Time to HRQoL score deterioration.
  – Toxicity (graded by National Cancer Institute -Common Terminology Criteria for Adverse Events (NCI-CTCAE) V.5.0).
► To quantify and compare the chemotherapy dose reductions, cumulative doses and study exit rates in the study arms.

Inclusion and non-inclusion criteria

Patients with CRC (stage II–III) starting adjuvant FOLFOX 4 will be eligible (see details in box 1).

Investigational medicinal product
Riluzole (Mylan, 50 mg, film-coated tablet)

Riluzole is indicated to extend life or to delay the use of mechanical ventilation in patients with ALS. It will be administered twice daily, 50 mg in the morning and in the evening. Riluzole will be started 1 week before and then concomitantly with oxaliplatin-based chemotherapy.

The dosage chosen corresponds to that reported in Grossman et al[42] and the summary product characteristics of riluzole.

Placebo

There is no gold standard preventive treatment for CIPN, so we have, according to actual recommendations, chosen to evaluate the therapeutic effect of riluzole in comparison to a placebo. To ensure the double-blind conditions, the placebo and riluzole will be packed in identical blister packs. Furthermore, the placebo tablets will have the same appearance as that of riluzole. Dosage, administration and duration of treatment will be identical to that of riluzole.

Study endpoints

The evaluation schedule is shown in figure 1.

Primary endpoint

The primary endpoint is the comparison of the sensory scale scores of the quality of life questionnaire-chemotherapy-induced peripheral neuropathy (QLQ-CIPN20) between the two treatment arms (placebo and riluzole) after six cycles of oxaliplatin-based chemotherapy (FOLFOX 4).

QLQ-CIPN20 (European Organisation for the Research and Treatment of Cancer (EORTC)). A self-reported questionnaire, consisting of 20 questions to assess the symptoms and functional limitations of CIPN from the patient's perspective. The questionnaire is divided into three subscales (sensory, motor and autonomic), and gives a comprehensive picture of the nature, frequency and severity of CIPN. The scores will be calculated according to the standard operating procedure of the EORTC and rated from 0 to 100.

This questionnaire has been validated by two large international clinical trials[49 50] and is recommended by ACTTION[35] for evaluating treatments to prevent CIPN. In addition, recent articles suggest that it is preferable to evaluate CIPN symptoms with patient-reported outcomes than clinician-reported outcomes and that

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Box 1   Inclusion and non-inclusion criteria of the study

Inclusion criteria
- ► Patients aged ≥18 years old.
- ► Eligible patient starting adjuvant oxaliplatin-based chemotherapy (FOLFOX 4) for stage II/III colorectal cancer.
- ► Histological or cytological confirmation of a colorectal cancer.
- ► PS (ECOG) ≤2.
- ► Normal hepatic function: total bilirubin ≤1.5 x ULN (unless documented Gilbert's syndrome), ASAT/ALAT ≤3 x ULN and GGT ≤3 x ULN.
- ► Normal renal function: creatinine clearance >40 mL/min or calculated creatinine clearance >40 mL/min (Cockcroft-Gault formula).
- ► Normal cardiac function, by ECG.
- ► Patients affiliated to the French national health insurance.
- ► Patient must have signed an informed consent form prior to any study-specific procedures.
- ► French language comprehension.
- ► Patient is willing and able to comply with the protocol for the duration of the study including undergoing treatment and scheduled visits and examinations including follow-up.

Non-inclusion criteria
- ► Metastatic cancer.
- ► Diagnosis of neuropathy prior to oxaliplatin-based chemotherapy.
- ► EORTC QLQ-CIPN20 sensory score >6/100.
- ► Previous neurotoxic chemotherapy treatment.
- ► Patients with chronic obstructive pulmonary disease.
- ► ALT/AST elevated more than three times the normal value.
- ► Patients with known allergy or severe hypersensitivity to riluzole or any of the study drug excipients.
- ► Dependence on alcohol or drugs.
- ► Psychotic disorders.
- ► Pregnant or breastfeeding women.
- ► Patients under legal protection (trusteeship, guardianship and so on).

ASAT, aspartate aminotransferase; ALAT, alanine aminotransferase; ECOG, Eastern Cooperative Oncology Group; EORTC, European Organisation for the Research and Treatment of Cancer; GGT, gamma-glutamyl transferase; QLQ-CIPN20, quality of life questionnaire-chemotherapy-induced peripheral neuropathy; ULN, upper limit of normal.ASAT, aspartate aminotransferase; ALAT, alanine aminotransferase; ECOG, Eastern Cooperative Oncology Group; EORTC, European Organisation for the Research and Treatment of Cancer; GGT, gamma-glutamyl transferase; QLQ-CIPN20, quality of life questionnaire-chemotherapy-induced peripheral neuropathy; ULN, upper limit of normal.

the QLQ-CIPN20 questionnaire is the most appropriate outcome measure.[51–53]

Only the sensory scale scores will be used to assess the primary endpoint. Based on the study published by Alberti et al,[54] the sensory scale scores of the CIPN20 questionnaire can be correlated with the neuropathy grade determined by the NCI-CTCAE as follows:

A sensory score CIPN20 of <30 as grade 0–1, a score ≥30 and ≤40 as grade 2 and a score >40 as grade 3–4.

Secondary endpoints

QLQ-CIPN20 (EORTC). Sensory, motor and autonomic scales during the study. See description above.

Neuropathic pain symptoms. The Neuropathic Pain Symptom Inventory (NPSI)[55] and the Brief Pain Inventory (BPI)[56] will be used to evaluate the characteristics and impact of neuropathic pain.

The NPSI is a self-administered questionnaire designed to assess different symptoms of neuropathic pain. This questionnaire includes 12 items that can discriminate and quantify five separate clinically relevant dimensions.

The BPI is a self-administered questionnaire that includes (1) a body scheme; (2) the maximum pain, lower pain and usual pain during the last 15 days (numerical rating scale (NRS) 11 points); (3) the description of the analgesic treatment in progress; (4) an evaluation of pain relief on a percentage scale (0%–100%) and (5) the impact of pain on mood, relationships with other people, walking, sleeping, work, joy of life and leisure activities (NRS, 0 normal to 10 impossible).

QLQ-C30 (EORTC). This self-reported questionnaire assesses the HRQoL of cancer patients in clinical trials. The questionnaire is divided into three subscales assessing global health status, functional scales (physical functioning, role functioning, emotional functioning, cognitive functioning and social functioning) and symptom scales/items (fatigue, nausea and vomiting, pain, dyspnoea, insomnia, appetite loss, constipation, diarrhoea and financial difficulties). The scores will be calculated according to the standard operating procedure of the EORTC and rated from 0 to 100.

NCI-CTCAE V.5.0. The NCI-CTCAE V.5.0 is widely accepted to grade adverse events in oncology clinical trials. This scale will grade the severity of sensory neuropathy.

Time-to-event endpoint (disease-free survival, overall survival and time to treatment failure):

    Disease-free survival, defined as the delay between the date of randomisation and the date of cancer relapse (local, regional or second cancer) or death from any cause, whichever occurs first.

    Overall survival, defined as the interval between the date of randomisation and the date of death from any cause.

    Time to treatment failure, defined as the delay between randomisation and treatment discontinuation for any reason, including disease progression, treatment toxicity, patient preference or death.

Time to HRQoL score deterioration. HRQoL will be evaluated using the QLQ-C30 at baseline and at each planned visit until the end of the study or death. Functional scale, symptom scale, global health status and financial difficulties were analysed in QLQ-C30. The time of deterioration was defined as the time interval between randomisation and the first decrease in HRQoL score ≥5 points with no further improvement in HRQoL score ≥5 points or any further HRQoL data.[57]

Adverse effects related to cancer, chemotherapy and study treatment. Adverse effects will be assessed (type, frequency, intensity and whether related to study treatment) by patients (in patients diary or during telephone follow-ups) and by investigators (during the

chemotherapy cycles and planned visits) throughout the study and graded by NCI-CTCAE V.5.0. The unblinding of treatment will be authorised in cases of serious adverse effects.

Quantification of chemotherapy dose reductions, discontinuations, cumulative doses and study exit rates. The number of chemotherapy dose reductions, discontinuations, cumulative doses and study exit rates, caused by severe neuropathy and/or poor tolerance of the treatment will be recorded.

Quantification of analgesics consumption for neuropathic pain. No concomitant treatment is prohibited. Details concerning the use of analgesics, regardless of the indication, will be collected during the study and their use will be compared in the two arms.

Ancillary study (see online supplementary information for details). Determine the evolution of the plasmatic glutamate levels during the study (at visits 0, 2, 3 and at the last follow-up visit). The data will be compared in the two treatments arms. First, the prognostics value of glutamate levels correlated with CRC TNM scores in CRC patients will be assessed. Second, we will investigate a possible correlation between blood glutamate levels and the intensity of neuropathic disorders. This investigation may open up new avenues for research.

Methodology and study design
Enrolment
The investigator will contact potential patients to discuss the study and their willingness to participate. If they are willing to participate, an appointment will be made for the inclusion– randomisation visit. The study design is shown in figure 1.

Patients will be recruited in at least 20 cancer centres, each with a large potential for recruiting patients and with extensive clinical trial experience.

Period 1: Study treatment and chemotherapy
Visit 0: Inclusion–randomisation
The study, including the objectives, organisation, constraints and assessment questionnaires will be presented to the patient. Prior to any study procedure, the patient will sign an informed consent form to confirm their willingness to participate in the study.

The following will be performed:
► Planning of chemotherapy (FOLFOX4) and scheduling of the study visits.
► Clinical examination (height, weight, performance status (Eastern Cooperative Oncology Group), vital signs, ECG), scanner and blood tests.
► Verification of patient's eligibility (inclusion and non-inclusion criteria).
► Randomisation (riluzole or placebo).
► Completion of study questionnaires (QLQ-CIPN20, QLQ-C30 and BPI).
► Delivery of study treatment (riluzole or placebo) to be started 1 week before chemotherapy and for at least six cycles of chemotherapy.

Visit 1: Start of FOLFOX 4
This visit corresponds to the routine visit at the start of chemotherapy. No additional assessments other than those routinely performed are planned. The patient will be reminded of the study procedures and treatment. Blood tests will be performed to verify that the patient will be able to support chemotherapy.

Visit 2: After six cycles of FOLFOX 4
The following will be performed:
► The patient will return the empty or unused study treatment.
► Clinical examination (including ECG).
► Tumour assessment by scanner.
► Pain assessment: BPI questionnaire, and if item 5 'general pain NRS' ≥4, then a DN4 interview will be performed and NPSI questionnaire completed.
► Completion of study questionnaires (QLQ-CIPN20 and QLQ-C30).
► Evaluation of toxicity (adverse effects related to sensory neuropathy and those associated with chemotherapy, cancer and study treatment by NCI CTCAE V.5.0).
► Collect information concerning dose reductions and discontinuations due to neuropathy (if applicable).
► Blood sampling (routine pre-chemotherapy blood tests and glutamate dosage).
► Delivery of study treatment according to randomisation (placebo or riluzole) for the remaining chemotherapy cycles (maximum six additional cycles).

Visit 3: End of chemotherapy and study treatment
The visit will take place 4 weeks after the last chemotherapy cycle (either completion of planned chemotherapy or discontinuation of oxaliplatin due to toxicity).

The following will be performed at the visit:
► The patient will return the empty or unused study treatment.
► Clinical examination.
► Pain assessment: BPI questionnaire, and if item 5 'general pain NRS' ≥4, then a DN4 interview will be performed and NPSI questionnaire completed.
► Completion of study questionnaires (QLQ-CIPN20 and QLQ-C30).
► Evaluation of toxicity (adverse effects related to sensory neuropathy and those associated with chemotherapy, cancer and study treatment by NCI CTCAE V.5.0).
► Collect information concerning dose reductions/discontinuations due to neuropathy (if applicable).
► Blood sampling (routine pre-chemotherapy blood tests and glutamate dosage).

Period 2: Post chemotherapy follow-up
These visits correspond to the routine/standard patient visits at 3, 6, 9 and 12 months after the chemotherapy.

The following will be performed:

► Pain assessment: BPI questionnaire, and if item 5 'general pain NRS' ≥4, then a DN4 interview will be performed and NPSI questionnaire completed.

► Completion of study questionnaires (QLQ-CIPN20 and QLQ-C30).

► Blood sampling for glutamate dosage.

► Evaluation of toxicity (adverse effects related to sensory neuropathy and those inherent to chemotherapy, cancer and study treatment by NCI CTCAE V.5.0).

Participants are allowed to withdraw from the study at any time without justification. Participants may also be withdrawn from the study in the event of non-compliance with the protocol (study visit and treatment compliance).

Statistical considerations
Sample size estimation

The required number of subjects is based on the comparison of QLQ-CIPN20 score (particularly, the 100-points sensory scale) between the two treatment groups (riluzole and placebo). Since no evidence concerning the anticipated efficacy exists, sample size is estimated according to conventional effect size (ES) thresholds reported by Cohen[58] for the Student's t-test: small (ES=0.2), medium (ES=0.5) and high (ES=0.8). For an ES of 0.5, 86 subjects per group will be required for a two-sided type I error of 5% and a power of 90%. Considering a 20% dropout rate, 105 patients per group will be required. Thus, the study will require a total of 210 patients. The study was designed to have the power to detect moderate differences, and is similar to that used to study venlafaxine.[59] Under these conditions, the results would appear to be statistically and clinically relevant.

Interim analysis

Our estimated sample size is not based on robust data, with respect to the QLQ-CIPN20 sensory scale scores and the estimated expected difference between arms. Thus, an interim analysis is planned for ethical and methodological reasons, in particular to be able to estimate effect size and statistical power. The type I error will be adjusted using the Lan-DeMets method (East, Pocock).[2] The interim analysis is planned after 21 patients in each arm (overall n=42) have been randomised, and the difference between study arms will be considered significant if α ≤0.015. An independent data monitoring committee (IDMC) will initially meet at the start of the study and then regularly during the study, and at minimum to discuss the results of the interim analysis. The committee will provide recommendations concerning the study conduct when required.

Statistical analysis

All analyses will be performed using Stata software (V.13, StataCorp, College Station, Texas, USA). The analysis will be performed on unblinded data in accordance with the *International Conference on Harmonisation-Good Clinical Practice* guidelines. Continuous variables will be presented as mean and SD or median and quartiles range, according to statistical distribution. These variables will be compared using the unpaired t-test or the Mann-Whitney U test when appropriate, according to assumptions of t-test: (1) the Shapiro-Wilk test will be used to assess normality and (2) the Fisher-Snedecor test to assess homoscedasticity. Categorical data will be presented as exact numbers and percentages. A two-sided p-value of <0.05 will be considered for statistical significance for all analyses.

The primary endpoint (the sensory score of the QLQ-CIPN20) will be compared by the Student t-test or the non-parametric Mann-Whitney if the conditions of the t-test are not met (study of normality, homoscedasticity studied by Fisher-Snedecor test). The results will be expressed as effect size and 95% CI. As recommended by Vickers and Altman, this analysis will be supplemented using analysis of covariance considering the baseline sensory score covariate. The primary analysis will be conducted on the intention-to-treat population. If appropriate, a complementary per-protocol analysis will be considered. These analyses will be completed by a multivariable approach. Multiple linear mixed regression will be carried out with covariates determined according to univariate results and clinical relevance, in addition to centre effect as random effect. The normality of the residuals will be studied using the Shapiro-Wilk test. If appropriate, a logarithmic transformation will be proposed to achieve the normality of the dependant outcome. The results will be expressed as regression coefficient and 95% CI. For other quantitative parameters (QLQ-C30, BPI, DN4 and NPSI questionnaires), the statistical analyses will be carried out in a similar way to that of the primary endpoint.

The categorical variables (proportion of chemotherapy discontinued or with dose reduction, as a result of severe neuropathy, incidence of motor and autonomic neuropathies, chemotherapy response, grade of sensory neuropathy) will be compared between groups by Chi-squared test or, if appropriate, Fisher's exact test. These analyses will be completed by multivariable approach using generalised linear mixed model (logistic regression) with covariates determined according to univariate results and clinical relevance. The results will be expressed as relative risks and 95% CI.

The study of repeated data collected longitudinally will be conducted by random-effects models (linear or generalised linear as dependent variable) to study the fixed effects, the evaluation time and interaction, while taking into account inter-patient and intra-patient variability (as random effect) in addition to centre random effect.[46]

The censored data (overall survival and disease-free survival) will be estimated by Kaplan-Meier method and will be compared between groups by the log-rank test for univariate analysis and Cox proportional hazards regression for multivariable analysis. The proportional hazard hypothesis will be studied using Schoenfeld's test and plotting residuals. For the time to HRQoL score deterioration, death will be considered as a competing risk. The

estimation will be performed using the Fine and Gray method. The adverse events related to cancer, chemotherapy and study treatment will be described.

Missing data

A sensitivity analysis will be conducted to study the statistical nature of missing data (missing at random or not). Accordingly, the most appropriate data imputation approach will be proposed: last observation carry forward, multiple imputation or estimations proposed by Verbeke and Molenberghs specifically adapted to repeated data.[47]

Randomisation and blinding

Randomisation (computer-generated random numbers), in a 1:1 ratio, will be performed by minimisation with stratification according to the following:

Centre.

CRC stage II versus III.

Study treatment will be allocated using e-CRF.

All participants, care providers, outcome assessors, data analysts will be blinded to treatment allocation (riluzole or placebo) after randomisation. The riluzole and placebo will have identical packaging to maintain the treatment blinding.

Unblinding will be allowed only in cases of serious adverse effects. If required, the sponsor will inform the pharmacist and investigator, by email within 24 hours of unblinding, whether riluzole or placebo corresponds to the number allocated.

Dissemination

Approval

We will submit all substantial modifications of the protocol and/or informed consent form to the ethics committee and/or competent authority for approval. The sponsor will notify the ethics committee and the competent authority of study termination. This study is registered in EudraCT and clinicaltrials.gov. The current protocol is V.1.1 (11 July 2018).

Patient informed consent

The investigator will discuss the study with the patient and provide the necessary information (both verbally and written). The patient may request further information or explanations concerning the study. Each patient will be given sufficient time to consider his or her study participation. If the patient agrees to participate, they will confirm that they freely and willingly accept to participate by signing and dating the inform consent form. The investigator will inform the patient that according to the data protection regulations their consent is required for the sponsor to directly access their personal data for the study. The investigator will inform the patient of their right to withdraw from the study at any time, at their own discretion and without necessarily giving a reason.

Data collection and quality management

At each participating centre, delegated site staff will be responsible for data entry and coding, and the secure storage of data. The patient's data will be pseudoanonymised. The data will be collected and managed using an electronic case report form. A clinical research associate, commissioned by the sponsor (UNICAN-CER-AFSOS group), will verify the data and monitor the study according to UNICANCER's standard operating procedures, good clinical practice and French laws. All participants, investigators, clinical research associates and pharmacists of each clinical centre will be blinded to study treatment. Biostatisticians will be blinded to treatment during all analysis.

An IDMC will be constituted for the study. The committee will consist of at least two clinicians, with expertise in OIPN, and a statistician/methodologist. These experts will be independent. The role of the IDMC is to ensure patient protection, ethical conduct of the study and evaluation of the benefit/risk ratio during the study. The committee will also review the data during the planned interim analysis.

Audits and inspections

The centre and investigators agree, by participating in the study, to allow and cooperate with audits and inspections. The sponsor, as part of its audit programme, may audit some of the investigational centres. The sponsor staff or any person duly authorised can perform these audits during the study and for at least 15 years after the study termination. In addition, the French competent authority can inspect the study, including the investigational centres. During an audit or inspection, the investigators must provide direct access to source data. They must devote sufficient time for the audit/inspection procedures, the control of data and the request for additional information by the auditors/inspectors.

Access to data and communication of results

The principal investigator (DP), biostatistician (BP) and the project managers (VP and NK) will have full access to the final data set. The results will be published in a peer-reviewed journal, presented at international congresses and summary results will be made publicly available via EudraCT and clinicaltrials.gov websites.

Patient and public involvement

The objective of the Federation of the Patient Committees for Clinical Research in Cancerology is to reviews trial documents provided to patients in oncology clinical studies. The committee makes recommendations to improve the quality of information given to patients. The 'Ligue Nationale Contre le Cancer' and the French NCI (INCa) coordinate this committee. The relevant trial documents for this study have been reviewed by this committee. In addition, the study has been registered in the EudraCT and the clinicaltrial.gov public registries. The study results will be published on these registries, when available. In addition, the study information will be available for patients on the 'Ligue Nationale Contre le Cancer' and INCa websites.

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