Study Protocol

A Phase II Open-Label Multi-center Trial of Isotoxic Hypofractionated Radiotherapy for NSCLC

ABSTRACT

Background: The standard treatment for advanced unresectable non-small cell lung cancer (NSCLC) is concurrent chemoradiotherapy. However, many poor KPS or elderly patients cannot tolerate it due to their serious side effects. For patients who cannot tolerate concurrent chemoradiotherapy, conventional treatment is sequential chemoradiotherapy or radiotherapy alone. But the median survival time of sequential chemoradiotherapy and radiotherapy alone is 11-16 months. In order to improve curative effect, radiotherapy, as an important treatment method, has been tried, innovated and improved continuously. The goal of this trial is to evaluate feasibility and safety of isotoxic hypofractionated radiotherapy in patients with NSCLC.

Methods: This is a phase Ⅱ open-label multi-center two-step non-randomised Trial. In the first stage, 12 patients will be included in the trial with radiotherapy of 3Gy per fraction. If m~~M~~ore than 3 patients had serious side effects of radiotherapy, the trial will be terminated. Otherwise, the second phase will continue, and the total number of participants will

beas 30. All patients eventually will be followed up for 5 years.

The primary endpoint is the safety of isotoxic hypofractionated radiotherapy. The secondary outcomes are time to progression (TTP), progression free survival (PFS), overall survival(OS), local control(LC).

Discussion: In clinical practice, the local control rate of conventional fractionated radiotherapy for NSCLC is very low. We hope that this trial can verify the safety of isotoxic hypofractionated radiotherapy.

Trial registration: NCT03606291, REGISTERED JULY, 30, 2018.

Keywords: Non-small cell lung cancer, Isotoxic hypofractionated radiotherapy

Introduction

Lung cancer seriously harms human health and is an important cause of human death. The standard treatment for advanced unresectable non-small cell lung cancer (NSCLC) is concurrent chemoradiotherapy[1-4]. However, many patients cannot tolerate it due to its severe side effects. A meta[5] analyzed from 3 prospective Radiation Therapy Oncology Group trials (RTOG 91-06, 92-04, and 94-10) in which concurrent chemoradiotherapy for good-Karnofsky performance status(KPS) NSCLC showed that 18% of patients had to discontinue radiotherapy because of acute side effects. It is still difficult for people with good KPS to perform concurrent chemoradiotherapy, not to mention those poor KPS or elderly

people. Driessen[6] reported that ~~O~~only 26% older patients can tolerate concurrent chemoradiotherapy, while sequential chemoradiotherapy reaches 40%. For patients who cannot tolerate concurrent chemoradiotherapy, Radiotherapy plays an irreplaceable role. In order to improve curative effect, radiotherapy, as an important treatment method, has been tried, innovated and improved continuously.

In the era before modern imaging and treatment planning design, randomized trials conducted by the radiotherapy Oncology Group (RTOG) showed that a standard treatment dose of 60-70 Gy was established using conventional fraction. But the standard dose of 60-70Gy for conventional fractionated radiation was not well controlled[7], the median survival time was only 11-16 months[3, 8-11]. So the dose escalation had been studied. Retrospective and non randomized prospective data suggested that further dose escalating in NSCLC might be associated with better outcomes. However, Schild[12] analyzed 3600 patients with locally advanced non-small cell carcinoma. It was found that conventional fractionated radiotherapy with dose above 60Gy did not improve survival, but was significantly related to the side effects of radiotherapy above grade 3, which could significantly increase the treatment-related mortality. So escalating doses by conventional fractionated radiotherapy was not the effective method to increase curative effect. The repopulation of cancer stem cells was one of the most important factors of radiation resistance [13].

That means the longer the overall treatment time , the less damage to the local tumor control [14]. So gradually increasing doses with conventional fraction did not improve overall survival as we wish.

Because of the poor efficacy of conventional fractionated radiotherapy, the research on changing the fraction method has always been a research hot spot. There are usually two methods: hyperfractionated or hypofractionated radiotherapy. Hyperfraction means multiple smaller doses of radiotherapy daily, hypofraction means fewer fractions with larger doses radiotherapy daily. Both can increase the doses which can convert into the Equivalent Dose in 2 Gy/f (EQD2) and shorten the total treatment time. CHART[15] confirmed that hyperfraction was superior to conventional radiotherapy. ECOG 2597[16] found that there was a positive statistical trend indicating a survival advantage of hyperfraction radiotherapy over conventional radiotherapy. However, this highly fractionated dose approach poses great challenges. Din[17] retrospectively included 609 patients in 4 UK centers with 55 Gy in 20 fractions, found that 2 year overall survival was 50%. Some phase I-Ⅱ trials[18] [19-21] [22, 23] also confirmed the safety of hypofractionated radiation therapy.

Current general studies had adopted uniform prescription doses. However, uniform prescription doses radiotherapy resulted in individual dose deficiency as some patients could tolerate higher radiation doses without severe toxicity, but for others higher radiation doses were not

tolerated. Therefore, we need to perform individualized dose prescription according to maximum tolerated doses (MTD) based on normal tissue.

The MAASTRO (Maastricht Radiation Oncology clinic) in the Netherlands[24-26] study published well established results from prospective studies using individualized dose prescriptions. Patients were irradiated using an individualized prescribed total tumor dose (TTD) based on normal tissue dose constraints up to a maximal TTD of 79.2 Gy in 1.8 Gy fractions twice daily. Only sequential chemoradiation was administered. The median prescribed TTD was 64.8 Gy, grade 4 acute toxicity was 2.4% and grade 4 late toxicity was 1.8%. No patients developed grade 5 toxicity. Individualized prescribed TTD based on normal tissue dose with sequential chemoradiation showed well survival rates that come close to results of concurrent chemoradiation schedules, with acceptable acute and late toxicity. Haslett[27] reported a multicenter clinical study in which 37 patients of Stage III Non-Small Cell Lung Cancer were recruited. Radiation dose was increased until a maximum dose of 79.2 Gy in 1.8 Gy fractions twice daily was reached or 1 or more of the organs at risk met predefined constraints. A maximum dose of 79.2Gy was achieved in 37.8%. Grade 3 esophagitis was reported in 2 patients, and no patients developed grade 3 to 4 pneumonitis. But there were 3 grade 5 events: acute radiation pneumonitis, bronchopulmonary hemorrhage, and acute lung infection. The treatment-related death rate was 5.7%. Its severe toxic side

reaction was acceptable, although exceeding that of the MAASTRO trial.

However, considering the time consuming and effort of accelerated hyperfraction radiotherapy, clinical operation was difficult. As an alternative to accelerated hyperfraction radiotherapy, it can alsoe provide good therapeutic results by reducing the total treatment time and providing a high biological effective dose(BED). Landau[28]reported a multicenter phase I/Ⅱ clinical study in which 84 patients were recruited from eight centers: the first group received 65 Gy, 68 Gy and 71 Gy with the maximum safety limit for the esophagus, and another group received radiotherapy under the premise of ensuring the maximum safety limit of other organs (mainly the lung). The number of fractionation was 30 and the average tumor dose was 67.7Gy. 5 cases of grade 3 esophagitis and 3 cases of grade 3 pneumonia were observed in both groups. After 35 months of follow-up, the mean overall survival rate was 36.9 months. The overall survival rate and progression free survival rate were 87.8% and 72.0% at 1 year and 68.0% and 48.5% at 2 years, respectively. All the above experiments were isotoxic individualized treatment experiments. However, the isotoxicity or individualized designs were not as comprehensive as our experiment. They did not include all organs at risk or did not achieve full individualization. Our experiment draw from the experience of MAASTRO, using an individualized prescribed total tumor dose (TTD) based on normal tissue dose constraints up to a maximal TTD, but not

using accelerated hyperfraction radiotherapy. The goal of this trial is to evaluate feasibility and safety of isotoxic hypofractionated radiotherapy in patients with NSCLC.

Methods/design

Trial objectives

Primary objective

The primary objective is to evaluate the safety of isotoxic radiotherapy. The safety endpoint is the number of participants with treatment-related severe adverse events, defined as the Grade Ⅳ radiation esophagitis, Grade Ⅲ radiation esophagitis which results in interruption of radiotherapy for 7 days or more and Grade Ⅲ or above radiation pneumonitis[29].

Secondary objectives

The secondary objectives are to evaluate:

- PFS: survival defined by the time, in months, before recurrence or death at 5 years after enrolled in the trial.

- OS: survival defined by the time, in months, before death (for any reason) at 5 years after enrolled in the trial.

- TTP: survival defined by the time, in months, before tumor progression at 5 years after enrolled in the trial.

- LC: Percentage of patients without progression of the tumor which received radiotherapy at 3 and 5 years after enrolled in the trial.

Study population

Patients will be considered eligible according to the following criteria.

Inclusion criteria:

1. Pathological or cytological diagnosis confirmed non-small cell lung cancer;
2. clinical stage according to the 8th edition of American Joint Committee on Cancer（AJCC）, including stage Ⅲ without resectable or who when SBRT/SABR are not suitable;
3. Age18 or older[30];
4. Life expectancy≥3 months;
5. Karnofsky performance status≥ 60;
6. Blood routine is normal, liver and kidney function ≤ 2.5 times the upper limit of normal;
7. Sequential chemotherapy is allowed, before and/or after radiotherapy;

Exclusion criteria：

1. Serious medical complications included pulmonary fibrosis history, myocardial infarction within 6 months, heart failure with level Ⅱ and

above, uncontrolled heart failure, uncontrolled COPD, uncontrolled diabetes patients, etc.

2. Others who are not suitable for hypofractionated radiotherapy.

Trial design

The present trial is a phase Ⅱ open-label multi-center two-step non-randomised trial. Three centers in the China are participating in this trial (The Second Hospital of Hebei Medical University, North China Petroleum Bureau General Hospital of Hebei Medical University, No.1 Hospital of Shijiazhuang City). The aim of the study is evaluating the safety of isotoxic hypofractionated radiotherapy for patients with stage Ⅲ NSCLC accord to inclusion and exclusion criteria. 12 patients are planned to be enrolled in first step and 18 patients are planned to be enrolled in second step. (Fig.1) The two-steps based on Simon's Optimal two-stage design[31]. Twelve patients in the first step will stop the trial if one of the following conditions were ~~met~~meeted~~d~~:

1) 4 or more patients have grade Ⅲ or above radiation pneumonitis.
2) 4 or more patients have grade Ⅳ and above radiation esophagitis, and/ or radiation esophagitis of grade Ⅲ cause radiotherapy interruption for more than 1 week[29].

In order to recruit patients, we set up publicity boards for recruiting patients in outpatient clinics and wards.

Study process

The trial schema is illustrated in Fig.2.

Baseline examination

At baseline, patients will undergo fiberoptic bronchoscopic biopsy or percutaneous lung biopsy , routine tumor biopsy, chest enhancement computed tomography(CT), upper abdomen CT, whole body bone scan, Brain magnetic resonance imaging(MRI), electrocardiogram(ECG), positron emission tomography /Computed Tomography (PET/CT) if the patient requests, blood carcinoembryonic antigen (CEA), blood Squamous cell carcinoma antigen (SCC), blood neuron-specific enolase (NSE), blood Glycoantigen 125 (CA125), blood cytofragmented 19 keratin (cyfra 21-1), blood routine, blood biochemistry, coagulation routine, plasma D-dimer, urine routine, stool routine.

Interventions

Isotoxic hypofractionated radiotherapy is a special type of radiotherapy that uses a hypofractionated method to give individualized doses to the tumor, at the same time ensuring normal tissue dose within the normal range. Its requirements are as follows:

1. Fraction mode: 3Gy/f.
2. Rradiotherapy techniques: Intensity Modulated Radiation Therapy (IMRT). Image Guided Radiation therapy (IGRT) at least once a week.
3. Breathing control: there is no requirements for 4D-CT or respiratory

gating technology, but 4D-CT will be encouraged. Patients undergoing pre-radiotherapy training should try to calm their breathing.

4. Imaging/localization: a planning CT scan will be performed with intravenous contrast injection. Patients will be scanned and treated, in the supine position with arms cross above their head, and immobilization with thermoplastic device or vacuum cushion as per local protocols, in order to properly limit the respiratory movement. The scan will fully include target and all organs at risk. CT scans layer thickness 5 mm and scan range begin from cricoid cartilage (including full neck if special conditions), and the lower bounds consisted of complete lungs and liver. Image data is input into the IMRT planning system. The target area will be~~is~~ outlined in the plain scan image sequence, and enhancement image sequence fusion will be~~is~~ performed for reference. Non-small cell lung cancer target area delineation consensus: In the lung window (1600, -600 HU)[32] outline the target area of the primary lung lesion, in the mediastinal window (400, 20 HU) outline the mediastinal target area, using the involved-field irradiation, not elective node irradiation.
5. Volume definitions: the Gross tumor volume (GTV) is the primary lung lesion and lymph nodes with a short diameter larger than 1 cm on CT, or lymph nodes with a short diameter less than or equal to 1 cm but PET/CT shows positive or biopsy confirmed; Clinical target volume

(CTV) is GTV expand 6mm (squamous and non-adenocarcinoma), or 8mm (adenocarcinoma), 3-5mm (metastatic lymph nodes) ; PTV was based on lung respiratory dynamics observed under a simulator. External expansion for CTV was 10-15 mm. The GTV was confirmed by two radiotherapists and one radiologist. Radiotherapists outline body contours and organs at risk. IMRT was performed using 5-7 coplanar or non-coplanar fields.

Comment [N1]: Use future tense in whole document while explaining study design

6. radiation therapy prescription and organ at risk(OAR) doses:

(1) isotoxic Individualized Dose:

A. With normal tissues and organs as a toxicity-limiting condition[29]: Spinal cord: 0%> 45 Gy, and≤ 2Gy each time, Lung: V20≤ 30%,V5≤ 65%, MLD≤ 16Gy, Esophagus: highest dose ≤ 72Gy.

B. Maximum limit: If the limit of any "A" is not reached, the maximum radiation dose is 72 Gy[22, 23].

(2) The lowest radiation dose: 45Gy.

7. Quality Assurance:

Prior to treatment, each patient's plan must be peer-reviewed, or approved by another radiation oncologist. All radiation treatment plans must meet target dose request for OAR. Before the plan is approved, the dose for each OAR must be verified by a physicist and an oncologist.

Clinical response evaluation(CRE)

Patients will undergo the first CRE immediately at the end of radiotherapy by CT chest, then undergo every 3 months after radiotherapy for the first 2 years, and every 6 months for the next 3 years. The results of CRT are according to response evaluation criteria in Solid Tumors(RECIST 1.1)[33].

Quality of life assessment

Each patient will be asked to fill in self-administered questionnaires (EORTC QLQ-C30 and LC13) to assess health-related quality of life (QoL). QoL will be assessed at baseline, 4 weeks after the beginning of radiotherapy and the end of radiotherapy.

Follow up

The first visit will begin at 1 month after radiotherapy. Patients will be seen every 3 months post radiotherapy for the first 2 years, and every 6 months until 5 years or death after treatment. At each visit, the history and physical examination will be conducted and recorded by oncologists, and adverse events (AE) of radiation pneumonitis and radiation esophagitis will be recorded. The EORTC QLQ-C30 (version 3) and LC13 quality of life questionnaire will also need to be completed.

Chest enhancement CT or PET/CT will repeated in each visit, upper abdomen CT, whole body bone scan, Brain MRI will repeated every 6 months. Disease recurrence or progression should be documented by appropriate imaging or biopsies. And we will specially arrange a follow-up doctor to remind patients to review by telephone.

Quality assurance

The trial will be performed in three centers. Patients will be recruited, treated and followed up at the radiation department of The Second Hospital of Hebei Medical University (China), North China Petroleum Bureau General Hospital of Hebei Medical University (China), No.1 Hospital of Shijiazhuang City (China). Then, at least two radiologists will check all the inclusion and exclusion criteria. Patients will be informed of the trial protocol and, on acceptance, will be enrolled into this trial. The trial will be open blinded because of the procedures employed and with an objective primary end point. The patient will be informed of the isotoxic hypofractionation group. Unacceptable treatment-related toxicity or adverse events which will be recorded in the case report form, must be judged by either the patient's treating physician or the chief investigator.

The radiotherapy target area and plan of the first two patients in each center need to be approved by the three centers before treatment. The data entry will be checked by two people, and the case report forms will be

locked in the filing cabinet. The chief investigator will review all case report forms every six months.

Statistical analysis

The study primary end point is the safety of isotoxic hypofractionated radiotherapy. We use the PASS software to calculate the sample size according to the Simon optimal two-stage designs for phase Ⅱ clinical trials[31]. The study design is with a two-sided alpha level of 0.125, and an estimated 85% power to detect increase in no radiotherapy side reaction patient of 15% i.e. 75% to 90%. Finally, we calculated that the result was 12 participants in the first step. More than 3 patients had serious side effects of radiotherapy, the trial will be terminated. Otherwise, the second step will continue, and the total number of participants was 30. Shedding, withdrawal and loss of follow-up cases will not be included in the statistical analysis. We will continue to include patients until the number of qualified patients reaches the experimental design.

Ethical and regulatory considerations

The trial has been submitted and approved by a research ethics committee in each of the participating hospitals, and received clinical trials authorisations from regulatory authorities. This trial was approved by the research ethics committee of the second hospital of Hebei Medical

University (2018-R099). The study will be conducted in accordance with ethical principles founded in the Declaration of Helsinki. If there is any important modification of the protocol, we will modify it on the official website of the clinical trial registration as soon as possible after the approval of the ethics committee. In each centre, the lead investigator will be responsible for identification, recruitment, data collection, completion of case report forms, follow-up of study patients and adherence to study protocol. Informed consent will be obtained from participants by the local lead investigator using a standard consent form and participant information sheet. Authorship will be defined as per International Committee of Medical Journal Editors guidelines. Results will be communicated at relevant international conferences, via publication and on the clinical trial registry. Data are collected using the individual trial case number on standard case report forms collated centrally by IHR and personal information will not be individually identifiable. The final trial dataset will be available to study investigators but will not be analyzed per centre.

Withdrawal criteria

Situations where a study treatment may need to be interrupted for other clinical reasons will be considered. If an interruption happened, the study chief investigator will be notified in advance, and further advice sought with regards to the appropriateness of restarting study treatment. Other

criteria for which treatment will be withdrawn include: disease progression before completion of study treatment; withdrawal of consent for treatment and/or study participation; pregnancy; and patient non-compliance.

Discussion

Isotoxic dose prescription was a new model in radiotherapy. The radiation dose was prescribed according to the tolerance dose of the nearby OAR. Meanwhile, the prescribed total tumor dose maximizes to the highest technically achievable level to increase the probability of tumor control. The strategy has the potential to overcome several limitations of conventional radiotherapy dose prescribing based on tumor volume, and is expected to increase the overall proportion of treatments for tumor control without severe toxicity [34].The individualized radiation dose prescription is expected to further improve the efficacy of radiotherapy. In the future, further individualization of treatment may include patient specific factors, such as complications and biological tumor characteristics, such as hypoxia, growth factors and cytokines, gene changes and imaging data, giving personalized PTV boundaries and improving dose volume parameters and dose limits for patient tumor characteristics.

In conclusion, individual prescription radical radiotherapy based on normal tissue dose limitation has a good prospect. In addition, we expect

that the isotoxic individualized radiotherapy regimen can be safely applied with acceptable acute and late toxicity, which may be the basis of phase Ⅲ prospective randomized trials and ultimately prove the superiority of this individualized method.

Abbreviations

4D:Four dimensional; AE: Adverse Event; AJCC: American Joint Committee on Cancer; ALT: Alanine aminotransferase; BED: Biological effective dose; BID: Twice A Day; CT: Computed Tomography; CTV: Clinical Target Volume; Dmax: Maximum Dose; COPD: Chronic Obstructive Pulmonary Disease; EORTC: European Organization for Research and Treatment of Cancer;FEV1: Forced Expiratory Volume in 1 second; GTV: Gross Tumour Volume; Gy: Gray; ICORG: Ireland Co-operative Oncology Research Group; IMRT: Intensity-modulated radiation therapy; IGRT: Image Guided Radiationtherapy; KPS: Karnofsky; LC: local control; Mg: Milligram; Ml: Millilitre; MLD: mean lethal dose; NCI-CTCAE: National Cancer Institute Common Terminology Criteria for Adverse Events; MAASTRO: Maastricht Radiation Oncology; NSCLC: Non-small cell lung cancer; OAR: Organ at risk; OS: Overall Survival; OS: Overall survival; PET/CT: Computerised Tomography-Positron Emission Tomography; PTV: Planning Target Volume; PFS: Progress free survival; QoL: Quality of Life; RT: Radiation therapy; RTOG: Radiation Therapy Oncology Group; RTQA:

Radiotherapy quality assurance; SABR: Stereotactic ablative radiotherapy; SBRT: Stereotactic body radiotherapy; TNM: Tumor/Nodes/Metastases; TTP: Time to progression;

Ethics approval and consent to participate

The study will be performed in accordance with the declaration of Helsinkiand the Ethical Guidelines for Clinical Research by the Ministry of Health, Labor, and Welfare in China[35]. The trial has been submitted and approved by a multi-centre research ethics committee in each of the participating hospital, and received clinical trials authorisations from regulatory authorities (The Second Hospital of HMU: 2018-R099). written informed consent will be obtained from all patients.

Consent for publication

Not applicable.

Availability of data and materials

All information will be provided in the published articles.

5010 words.

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Figure legends

Fig.1 Methodology design of the IHR study

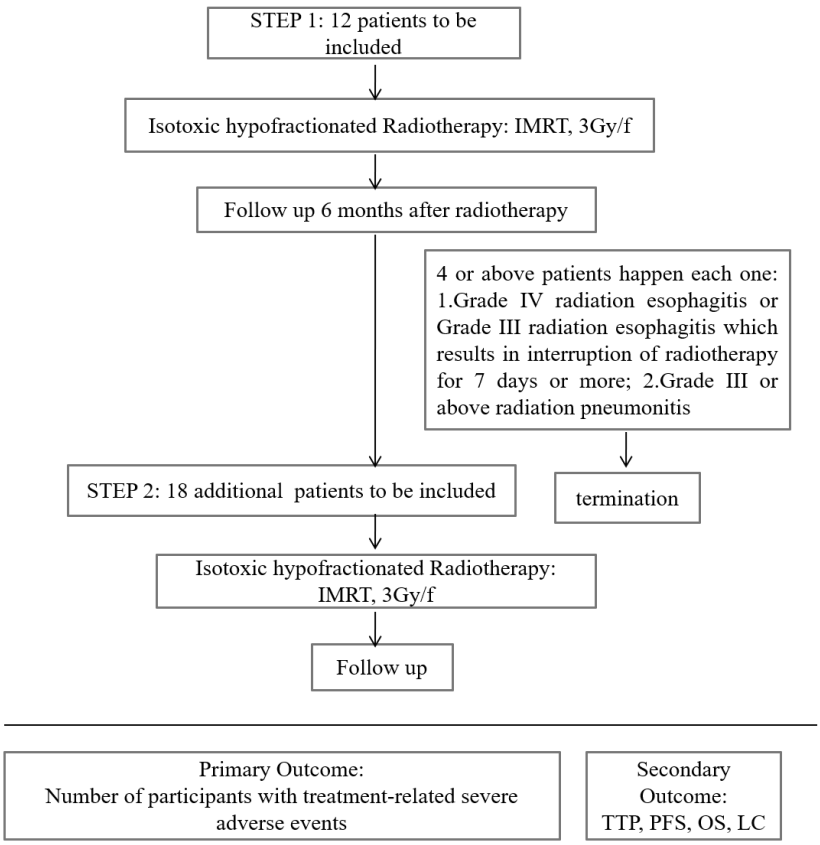
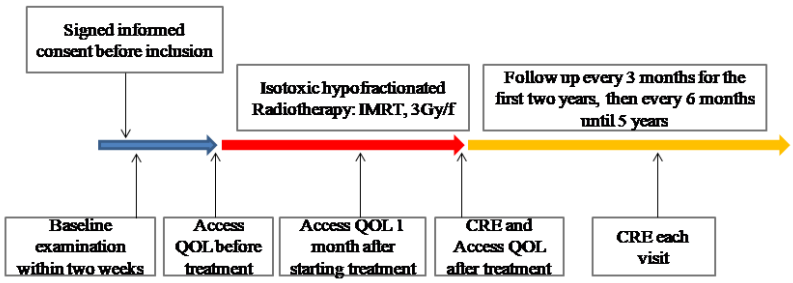


Fig.2 Schematic representation of the IHR study


Signed informed consent before inclusion
Isotoxic hypofractionated Radiotherapy: IMRT, 3Gy/f
Follow up every 3 months for the first two years, then every 6 months until 5 years
Baseline examination within two weeks
Access QOL before treatment
Access QOL 1 month after starting treatment
CRE and Access QOL after treatment
CRE each visit