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Health-related quality Of Life In patients with advanced Soft TIssue sarcomas treated with Chemotherapy (The HOLISTIC study): protocol for an international observational cohort study

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ABSTRACT

Introduction Chemotherapy is the mainstay of treatment for patients with advanced soft tissue sarcomas (STS). Treatment intent is usually palliative, aiming to improve symptoms, stabilise or reduce tumour burden and extend life. Clinical trials have traditionally used radiological response, time to progression and survival as measures of treatment efficacy. Health-related quality of life (HRQoL) is at least equally important or more important than survival for many patients with advanced cancer. Systematically collecting HRQoL data during chemotherapy can provide greater insight into treatment efficacy from the patient perspective.

The primary aims of this study are to evaluate HRQoL in patients with advanced STS treated with chemotherapy over time, explore the decision-making process and patient reflection post-treatment.

Methods and analysis This is an observational, international cohort study for 132 patients aged ≥18 years with advanced STS treated at eight centres (three in the UK, five in the Netherlands). Patients will be recruited prior to starting first-line or third-line chemotherapy and invited to complete questionnaires using the Patient-Reported Outcomes Following Initial treatment and Long-term Evaluation of Survivorship registry (PROFILES); an established international registry for collection of cancer patient-reported outcomes. Online (or paper) questionnaires will be completed at baseline, each cycle of chemotherapy and 2–3 monthly during follow-up. The questionnaire package includes the Decisional Conflict Scale, Control Preferences Scale, Quality–Quantity Questionnaire, treatment expectations, European Organisation for the Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC-QLQ-C30), EORTC financial toxicity items, Work Ability Index, Functional Assessment of Cancer Therapy-General (FACT-G) items and Decisional Regret Scale. Clinical data will be extracted from patient records and linked with questionnaire responses. The primary outcome measure is the change in global HRQoL from baseline to after cycle 4 of first-line chemotherapy (based on published data showing that patients with advanced STS complete a median number of four cycles of first-line chemotherapy).

Ethics and dissemination Heath Research Authority and Research Ethics Committee (REC 17/NI/0197). Results from the Health-related quality Of Life In patients with advanced Soft TIssue sarcomas treated with Chemotherapy (HOLISTIC) study will be published in peer-reviewed journals and disseminated at local, national and international conferences. We will also present our findings at any appropriate patient meetings and involve patients in study-related publications.

Trial registration number NCT03621332.

Strengths and limitations of this study

- Questionnaire data will be collected using the online Patient-Reported Outcomes Following Initial treatment and Long-term Evaluation of Survivorship system (PROFILES); a well-established electronic platform for the collection of patient-reported outcomes such as health-related quality of life (HRQoL).
- The longitudinal design of the study enables analysis of HRQoL across treatment lines.
- Although a validated HRQoL questionnaire specifically for patients with soft tissue sarcoma has not yet been developed, the study questionnaire package was developed in collaboration with patients and incorporates validated cancer-specific HRQoL questionnaires.

BACKGROUND

Soft tissue sarcomas (STS) are a group of rare and heterogeneous tumours, which account for approximately 1% of solid malignancies in adults.[1] Due to the rarity and diverse presentation of STS, diagnosis can be delayed and around 10% of patients will be present with metastatic disease.[2–5] Furthermore, many STS demonstrate an aggressive phenotype and approximately half of patients with intermediategrade or high grade localised tumours will develop metastatic disease after initial curative treatment.[3 6] Despite advances

in the treatment of many other cancers, the prognosis for patients with advanced, inoperable STS remains poor with a median overall survival of 12–19 months.[7 8]

Chemotherapy is the mainstay of treatment for patients with advanced STS. Other options include active surveillance for those with indolent or asymptomatic disease, radiotherapy or local therapies (eg, radiofrequency ablation or surgery) for patients with oligometastases, and best supportive care for those with end-stage disease and poor performance status (PS).[6] The principal aims of chemotherapy are to ameliorate symptoms, slow or halt tumour growth and prolong survival.[9] Standard first-line treatment, for the majority of STS subtypes, is anthracycline-based chemotherapy (usually doxorubicin), administered 3weekly up to a maximum of six cycles due to the risk of cumulative cardiotoxicity. The combination of doxorubicin with ifosfamide is associated with higher response rates and longer progression-free survival, however with no improvement in overall survival and at the expense of increased toxicity.[10] Doublet therapy may be considered for certain patients in whom a rapid response is clinically desirable, such as those with highly symptomatic chemosensitive disease.[10] Other first-line chemotherapy regimens include weekly paclitaxel for patients with angiosarcoma and (rarely) low dose cyclophosphamide±prednisolone for frail, often elderly patients.[11 12] A number of systemic agents are available following first-line anthracycline-based therapy, including trabectedin, pazopanib, gemcitabine±docetaxel, dacarbazine and eribulin.

Radiological response to first-line chemotherapy for advanced STS ranges from 10% to 50% (according to response evaluation criteria in solid tumours (RECIST V.1.1)), and is dependent on patient-specific-factors (eg, PS), tumour histology and chemotherapy regimen.[6] Treatment decisions are often challenging due to modest response rates and potential treatment-related adverse side effects. For many patients with advanced cancer, health-related quality of life (HRQoL) is equally important or more important than survival when making treatment decisions.[13 14] HRQoL is a multidimensional concept that represents the patient's perception of a disease and its treatment on physical, psychological and social aspects of their life.[15] Systematically collecting HRQoL data over time may provide greater insight into treatment efficacy from the patient perspective and may enable a more detailed assessment of the risk–benefit ratio of chemotherapy for each individual patient.[16]

The efficacy of systemic therapies in patients with cancer has traditionally been evaluated with dimensional radiological response, progression-free survival and overall survival. The burden of symptoms in patients with advanced STS is high, particularly pain and dyspnoea.[17] Despite the high symptom burden and palliative intent of treatment for most patients with advanced STS, the degree to which chemotherapy reduces symptoms of disease, improves or stabilises daily functioning and impacts HRQoL has rarely been measured or incorporated in the main endpoints of clinical trials.[15] Collecting patient-reported outcomes (PROs), such as HRQoL, is increasingly recognised to be key to fostering patient-centred care and influencing clinical decision-making.[18] Patients' perspectives can also influence treatment decisions in an era of rising treatment costs and limited resources. Collection of PROs during chemotherapy has been well described.[19 20] Patient self-reporting improves symptom detection as clinicians frequently underestimate toxicities associated with systemic chemotherapy.[20 21] Recording electronic PROs in real time can also improve HRQoL, patient–provider communication, reduce hospitalisation and improve survival.[22]

Existing research into the HRQoL of patients with sarcoma has primarily focused on survivors of localised extremity STS, or specific subgroups of patients with advanced STS.[23–26] For example, the SABINE study evaluated HRQoL among patients with metastatic STS or bone sarcoma who had attained a favourable response to chemotherapy.[27] The PALETTE trial of pazopanib versus placebo, as second-line treatment (or greater) for patients with advanced STS, evaluated HRQoL as an exploratory endpoint.[28] Although pazopanib did not improve HRQoL, meaningful improvement in progression-free survival was demonstrated with no associated impairment of HRQoL[28] Hugdens *et al* analysed HRQoL for patients with advanced STS treated within the phase 3 trial of eribulin versus dacarbazine.[29] This analysis demonstrated lower global health status and physical functioning scores, significantly worse loss of appetite, nausea and vomiting and insomnia in patients treated with dacarbazine on progression compared with patients treated with eribulin.[29] The REGOSARC study of metastatic STS patients refractory to doxorubicin, posthoc quality-adjusted survival benefit analysis demonstrated superiority of regorafenib over placebo.[30] The SARC021 phase 3 trial of doxorubicin versus doxorubicin plus evofosfamide reported no difference in HRQoL between treatment arms, despite a higher incidence of adverse events in the combination treatment arm.[8] The phase 3 randomised study of trabectedin versus dacarbazine in patients with metastatic leiomyosarcoma or liposarcoma after failure of conventional chemotherapy used patient-reported symptom scoring.[31] A variety of HRQoL instruments were used to collect data in these studies as no specific HRQoL tool exists for STS—primarily due to the heterogeneity of this group of patients.[16 26]

In order for patients with advanced STS to make a well-informed decision about chemotherapy and consider the possible effects on all aspects of their lives, clinicians should be able to provide HRQoL data. This will enhance the shared decision-making process between clinicians and their patients. To the best of our knowledge, this is the first study for patients with advanced STS which will evaluate HRQoL across chemotherapy treatment lines, consider the decision-making process (expectations and preferences for quantity of life vs QoL) and explore decisional regret.

METHODS/DESIGN

The Health-related quality Of Life In patients with advanced Soft TIssue sarcomas treated with Chemotherapy (HOLISTIC) study is a longitudinal cohort questionnaire study for patients with advanced STS treated at eight sarcoma centres: three in the UK and five in the Netherlands (NL). The principal aim of this study is to assess how first-line chemotherapy affects global HRQoL over time (specified below) in patients with advanced STS. This study also aims to assess patient functioning (physical, psychological, emotional, social and role) and symptoms, before, during and after treatment with chemotherapy. The study will also explore treatment decision-making (expectations and preferences), financial toxicity of treatment and decisional regret after treatment. Detailed outcome measures are defined below.

Patient and public involvement

The study concept was developed in consultation with patient advocates, patients and their relatives, who felt that there was a lack of information on HRQoL in patients receiving chemotherapy for advanced soft tissue sarcoma in order to make a well-informed decision about treatment. Study documents were reviewed by the patients who are members of the Royal Marsden Hospital Patient and Public involvement panel. The panel provided feedback on the protocol, questionnaires, patient information sheet and informed consent form, with regard to content and readability. All suggestions were considered and changes incorporated in the final documents. In order to reduce time burden for patients, the questionnaire package was designed to minimise questionnaire fatigue. Patients will be involved in study-related presentations and publications.

Eligibility criteria and materials

Inclusion criteria

Eligible patients must be aged ≥18 years with a diagnosis of advanced (not amenable to curative surgical resection) or metastatic STS, as confirmed by a sarcoma histopathologist, and has decided to start palliative chemotherapy following consultation with their oncologist. Patients must be enrolled prior starting first-line chemotherapy or third-line chemotherapy. Patients must be able to communicate in English or Dutch, and have mental capacity to provide informed consent and participate in the study (as determined by their treating physician). Patients must be able to complete questionnaires themselves, which is a prerequisite for patient-reported outcomes. Participants must be treated at one of the participating centres.

Exclusion criteria

Due to significantly different treatment protocols, patients with Ewing sarcoma, rhabdomyosarcoma, desmoplastic small round cell tumour and gastrointestinal stromal tumour are not eligible for the study.

Data collection

Data collection and online questionnaire administration will be done within the 'PROFILES' registry (Patient-Reported Outcomes Following Initial treatment and Long term Evaluation of Survivorship; www.profilesregistry.nl). The 'PROFILES' registry was established in the Netherlands (2009) for the study of the physical and psychosocial impact of cancer and its treatment in short-term and long-term cancer survivors.[32] Since PROFILES has been established, studies have recruited over 30 000 patients, resulting in more than 100 scientific publications. Security of the PROFILES server is established in accordance with current European norms (NEN-ISO/IEC 27002). Questionnaire data which are collected from participants (UK and NL) through the PROFILES registry is stored on a secure server in the Netherlands. This application has been developed to the requirements of the higher education and research community using end-to-end encryption.

Recruitment

Patients will be identified by a member of the sarcoma team who will check eligibility criteria using electronic patient records. Patients will be invited to participate in the outpatient clinic, provided with a patient information sheet and given the opportunity to ask any questions to a member of research team. Interested patients will be given the option to participate online or using paper versions of the questionnaire. Those who prefer online participation will receive an email which includes a link to the secure PROFILES website, unique username and password. The US Food and Drug Administration have made it clear that electronic capture of clinical trial source data is preferred over paper-based data collection.[33] There is now widespread use of electronic patient reported outcome measures (PROMs) within clinical trials, and several reviews and meta-analyses have shown evidence of equivalence between electronic and paper administration of PROMs.[34 35] In order to ensure that patients are not excluded if they are unable to use a computer, we have provided the option for paper questionnaire completion. Paper copies of the questionnaires will be entered using the data entry option of PROFILES, after which a quality control check will take place. This online data entry portal minimises the chance of errors as the answer options are selected from electronic lists. This also ensures that the paper questionnaire data can be extracted in the same format as the online questionnaire data. The PROFILES data manager will randomly choose five participants who have completed paper questionnaires and check the data entry for complete accuracy. If any errors are found, then all data will be rechecked and corrected where necessary.

All participants will complete an informed consent form. This can be done electronically (using PROFILES personal login details) or on paper if the patient prefers a hard copy. Patients are assured that non-participation has no consequences for their treatment or follow-up care.

After informed consent, patients will be invited to complete the online (or paper) baseline questionnaire. This must be completed before starting first-line chemotherapy or third-line chemotherapy (third-line patient cohort). Patients can complete the online questionnaire on their own computer, tablet or mobile phone, or using a hospital computer if available. Patients who have completed the baseline questionnaire will then receive an email on day 1 of each cycle of chemotherapy, inviting them to complete a new questionnaire using their existing login details (usually every 3 weeks). Patients who prefer paper versions will be handed a hard copy of the questionnaire in the chemotherapy clinic, with the option to return this by mail using the prepaid envelopes provided, or hand to the research team in a sealed envelope. If chemotherapy is delayed for any reason, patients will be invited to complete the questionnaire when treatment has restarted. Baseline questionnaires will take around 20 minutes to complete and subsequent questionnaires will take around 10–15 minutes. Patients will complete a maximum of eight questionnaires during chemotherapy to reduce the potential for questionnaire fatigue. Patients have a 2-week period to complete each questionnaire and will be sent an electronic or paper reminder after 1 week if they have not completed a questionnaire.

When a participant stops first-line chemotherapy, or third-line chemotherapy (respective cohorts), for any reason (eg, all cycles completed, or disease progression), he/she will be invited to complete an 'end of chemotherapy' questionnaire. Patients will receive this invitation approximately 3 weeks after the last dose of chemotherapy. Thereafter, patients who have received first-line chemotherapy will be invited to complete 3 monthly follow-up questionnaires, and patients in the third-line chemotherapy cohort will complete 2 monthly follow-up questionnaires (due to the shorter prognosis). If a participant starts a new line of chemotherapy (eg, second-line chemotherapy) during the follow-up period, he/she will remain on the same follow-up schedule of questionnaires in order to follow the trajectory of their HRQoL during second-line treatment and beyond. Due to concern about questionnaire fatigue, it was felt that patients who had already completed 3-weekly questionnaires during first-line chemotherapy should remain on the 3 monthly follow-up schedule, rather than receiving questionnaires at the beginning of each cycle of second-line chemotherapy. Due to the time frame of the study, we will simultaneously recruit patients beginning third-line treatment to explore HRQoL in patients with advanced STS who are further along their treatment trajectory.

Participants will be invited to complete follow-up questionnaires until he/she chooses to stop, is too unwell to continue or death occurs, whichever comes first, and up to a maximum of 2 years after study enrolment. Participants will only be enrolled once; either prior to first-line chemotherapy or before third-line chemotherapy. Throughout the study, it is the responsibility of the local sarcoma team to inform the study coordinator if a participant has died or is too unwell to continue.

Case report forms

After a patient has provided informed consent, clinical data will be collected from electronic patient records by a member of the research team. Data collection and storage will be maintained according to ICH-GCP (international good clinical practice) standards. Clinical details will be entered into the password protected database (MACRO) and stored using an anonymous patient identifier number. Personal identifiable clinical data of the patient will not leave the hospital where the patient is treated.

Case report forms (CRF) will be completed at four timepoints during the study. The first CRF should be completed after patient consent, and includes documentation of eligibility criteria, date of diagnosis of sarcoma, histological subtype and chemotherapy treatment regimen. The second part of the CRF should be completed when a patient stops first-line chemotherapy (or third-line chemotherapy for the third-line cohort). Information gathered at this timepoint includes reason for discontinuation of chemotherapy (eg, disease progression). The third point for CRF completion occurs when a patient stops participation in the study (eg, patient preference) and includes details of all chemotherapy regimens received during the study. The final point for CRF data collection is death notification, where applicable.

At the end of the study, questionnaire data will be linked with the clinical data contained within the CRF database using patient study numbers. Data linkage will be done by the study statistician at the Royal Marsden Hospital. Data will be recorded and retained in accordance with the Data Protection Act 1998.

Questionnaires

The baseline questionnaire contains questions on sociodemographic characteristics of the participant, such as marital and occupational status. Patients will also be asked a single screening question on health literacy which has validated among cancer patients and used in previous Dutch studies.[36 37]

The following internationally validated questionnaires and published questionnaires in studies of cancer patients will be used. These questionnaires have not been specifically validated in patients with advanced STS, however no STS-specific questionnaire has been developed to date. Permission to use all questionnaires has been obtained from authors. Formal licences are not required. Patients were involved in the design and review of the questionnaire package. All questionnaires were available in English. The Dutch questionnaire package was developed using validated Dutch versions of the questionnaires where possible or existing online Dutch translations of the questions. Where existing translations were not available, bilingual speakers assisted with formal

foward–backward translation of questions and discrepancies resolved by OH (details below).

EORTC-Quality of Life Questionnaire (EORTC-QLQ-C30)

The European Organisation for the Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC-QLQ-C30) V.3.0 was developed to assess QoL in patients with cancer. It has been translated and validated in over 100 languages, including English and Dutch. This questionnaire has 30 items, consisting of five functional scales (physical, role, cognitive, emotional and social), a global quality of life scale, three symptom scales (fatigue, pain, nausea and vomiting) and single items assessing common symptoms (dyspnoea, loss of appetite, sleep disturbance, constipation and diarrhoea) and perceived financial impact of the disease.[38] After linear transformation, all scales and single-item measures range in score from 0 to 100. A higher score on functional scales and global QoL means better functioning and HRQoL, whereas a higher score on the symptom scales means more complaints.[38]

Financial toxicity

Financial toxicity questions were selected from the item bank of the EORTC computer adaptive testing instrument and are validated in both English and Dutch languages.[39] In combination with the EORTC-QLQ-C30 questionnaire, these questions will maximise information surrounding the financial impact of advanced STS and its treatment. This is particularly relevant for patients with rare cancers, such as STS, who may need to travel long distances to receive care at a specialist centre.[40]

Functional Assessment of Cancer Therapy-General

The Functional Assessment of Cancer Therapy-General (FACT-G) is a validated questionnaire which has been widely used to measure HRQoL in patients with cancer. The FACT-G has been translated and validated in many languages including English and Dutch.[41 42] Patients are asked to rate their response to several statements on a 5-point Likert scale from 'not at all' to 'very much'.[41] We have selected two items from the FACT-G questionnaire:'I am bothered by side effects of treatment' and 'I am able to enjoy life' as a summary measure of the burden of a given set of toxicities.[43] Single items from the FACT-G questionnaire are not validated, however 'bother' from side effects has been shown to be associated with patients' ability to enjoy their lives.[43]

Control Preferences Scale

This validated questionnaire is designed to measure patients' preferred role in decision making versus their doctor's role.[44] Patients are asked to choose from five options the phrase that best describes the role that they have taken in dealing with their cancer diagnosis and treatment decisions, and the role that they would have preferred (active/collaborative/passive role).[44] Understanding patient preferences for control in treatment decision-making is crucial to improving shared decision-making and providing patient-centred care.[45 46] Dutch translations of the Control Preferences Scale are available and have been used in previous studies in the PROFILES registry.[47]

Decisional Conflict Scale

The Decisional Conflict Scale measures personal perception of decision-making, and certainty or uncertainty over their choice.[48] This includes determining the level of information and support to make the choice, whether the decision was in line with patient values and how satisfied they are/were with their decision. Items are given a score value of 0 (no) or 1 (yes). The total score can only be calculated if all four items are answered. The sum of the four items will range from 0 (extremely high decisional conflict) to 4 (no decisional conflict). A score of ≤3 indicates decisional conflict.[48] This four-item version of the Decisional Conflict Scale Questionnaire ('SURE') has been validated in English and a Dutch translation is available (psychometric properties have been partly confirmed in Dutch patients).[49]

Quality–Quantity Questionnaire

The Quality–Quantity Questionnaire (QQQ) tool is a validated construct consisting of eight questions which measure patient attitudes towards the trade-off of between quantity of life versus QoL (four questions for length of life (LOL) and four questions for QOL).[50] A separate score is calculated for LOL and QOL. The total score for all four questions (LOL or QOL) is calculated and the minimum score (4) is then subtracted. This answer is then divided by the range (20-4) to create a rescaling of 0–100. For example, if a person scores 3 (midpoint answer) for all four questions, the calculation would be: (12-4)/(20-4)=0.50 (midpoint overall score).[50] Decision-making in patients with advanced STS is extremely complex. Patient preferences for LOL and QOL are of utmost importance when weighing up the benefits and risks of treatments such as chemotherapy. Responses to these questions will allow insight into the preferences of patients with advanced STS and may help to inform shared treatment decisions.The original QQQ was written in the Dutch language (Professor Stiggelbout from the Netherlands) and has been translated and validated in English.[50]

Expectations of treatment

After the decision has been made to receive chemotherapy, patients are asked how likely they think that chemotherapy will improve survival, cure their cancer and improve symptoms due to cancer.[51] Studies in patients with other metastatic solid tumours have shown that patients often overestimate their life expectancy and many believe that chemotherapy will be curative.[51] Prognostic awareness has been associated with worse HRQoL in patients newly diagnosed with incurable (lung or GI) cancer.[52] This question will be used to assess expectations of chemotherapy among advanced STS patients. These questions were originally written in English and therefore

bilingual speakers performed a forward–backward translation of the questions into Dutch under the supervision of OH.

Work Ability Index

The Work Ability Index (WAI) consists of questions which assess the ability to work, taking into account the demands of the work, health status and resources.[53] There are seven questions from which we selected two general questions to inform future patients who are receiving chemotherapy on their potential ability to work during and after chemotherapy. These two questions are scored 0–10 and 1–6, respectively, and will be described in the analysis.[53] The WAI was developed in Finland and is available in 24 languages, including English and Dutch.[54] The validity and reliability of the WAI has been assessed in correlation analyses and used in many international research studies.

Decisional Regret Scale

Patients are asked to think about the decision they have made to receive chemotherapy and answer five statements on how strongly they agree/disagree: (1) it was the right decision, (2) I regret the choice that I made, (3) I would go for the same choice if I had to do it over again, (4) the choice did me a lot of harm and (5) the decision was a wise one.[55] Items 2 and 4 should be reverse-coded so that, for each item, a higher number will indicate more regret. To help others interpret the score more readily with other scales ranging from 0 to 100, these scores can then be converted to a 0–100 scale by subtracting 1 from each item then multiply by 25.[55] To obtain a final score, the items are summed and averaged. A score of 0 means no regret; a score of 100 means high regret.[55] The Decisional Regret Scale can be used to measure distress or regret after a healthcare decision such as the choice to receive chemotherapy. Regret about the decision to receive chemotherapy has not been previously measured in patients with advanced STS. The Decision Regret Scale is available in English and Dutch; Dutch translation by Leiden University Medical Center under supervision of Professor Dr Stiggelbout and Dr Pieterse, November 2010.[56]

Timepoints

Questionnaire A is the baseline questionnaire, which should be completed before starting chemotherapy.

Patients are invited to complete Questionnaire B on day 1 of cycle 1 of first-line chemotherapy or third-line chemotherapy (third-line cohort). Patients are invited to complete Questionnaire C on day 1 of every cycle from Cycle 2 onwards and 3 weeks after the last cycle of chemotherapy. Questionnaire D is the follow-up questionnaire which is completed every 3 months after the end of chemotherapy for first-line chemotherapy patients, and every 2 months for the third-line chemotherapy patient cohort. Patients have a 2-week window to complete each questionnaire and will be sent a reminder after 1 week if they have not completed the questionnaire. Table 1 summarises enrolment, timepoints, the questions which are included in each questionnaire and the number of questions in each questionnaire.

Endpoints

The primary endpoint is change in EORTC-QLQ-C30 global HRQoL score (continuous scale) after treatment with first-line chemotherapy. Secondary endpoints are change in EORTC-QLQ-C30 physical, cognitive, social, role and emotional functioning scores (continuous) after treatment with first-line chemotherapy, and change in EORTC-QLQ-C30 symptoms (continuous) after treatment with first-line chemotherapy.

The study will also explore change in EORTC-QLQ-C30 global HRQoL score, EORTC-QLQ-C30 functioning scales and symptom scores after treatment with third-line chemotherapy (third-line patient cohort).

For all patients, we will examine whether there is an association between sociodemographic and clinical factors (including age, gender, relationship status, educational level, PS, tumour subtype, site of metastases, baseline anaemia (Hb <13 g/L male, <11.5 g/L female), lymphopoenia $<1\times10^9$/L, lactate dehydrogenase (LDH) >250 U/L, hypoalbuminaemia <35 g/L) and baseline EORTC-QLQ-C30 global HRQoL and/or change in physical, cognitive, social, role and emotional functioning during and after treatment. The study will evaluate whether there is an association between HRQoL and radiological response (according to RECIST V.1.1) to chemotherapy, and between HRQoL and financial toxicity.

The study will explore work ability in patients with advanced STS treated with chemotherapy, patient preferences for collaborative decision-making, decisional conflict about treatment, expectations of treatment with chemotherapy, preferences for quantity of life versus QoL and retrospective views on their decision to receive chemotherapy.

Statistical analysis and power calculation

Primary endpoint

Change in EORTC-QLQ-C30 global HRQoL score will be tested using a paired sample t-test from baseline to after four cycles with a two-sided 5% significance level. For patients who do not complete four cycles, the last score/observation (post baseline) will be carried forward for the analysis. Four cycles was chosen as the timepoint for the analysis based on a study of 488 patients with advanced STS treated at the Royal Marsden Hospital, showing that patients completed a median number of four cycles of chemotherapy (range 1–8).[57]

A sensitivity analysis will also be performed excluding those patients who do not reach four cycles.

If data are not normally distributed, then the Wilcoxon test will be used.

Secondary endpoints

Differences in physical, cognitive, social, role, emotional functioning and symptoms from baseline measurements

Table 1 Enrolment and schedule of questionnaires

Timepoint	Enrolment	Baseline	Cycle 1 chemotherapy	Cycles 2–8, and end of chemotherapy	Follow-up
Eligibility screen	X				
Informed consent	X				
QUESTIONNAIRES (number of items)		Questionnaire A	Questionnaire B	Questionnaire C	Questionnaire D
Sociodemographic questions (15)		X			
Health literacy (1)		X			
Control Preferences Scale (2)		X			
Decisional Conflict Scale (4)		X			
Quality Quantity Questionnaire (8)		X	X	X	
Expectations of treatment (3)		X	X	X	–
EORTC-QLQ-C30 (30)		X	X	X	X
Work Ability Index (3)		X	X	X	X
EORTC CAT items: financial difficulties (5)		X	X	X	X
FACT-G items (2)		–	X*	X	X
Decisional Regret Scale (5)		–	–	X	X
Total number of questions		71	50	56	45

*FACT-G, cycle 1 questionnaire includes the single statement 'I am able to enjoy life'. Cycles 2–8 and follow-up questionnaires include the additional statement 'I am bothered by the side effects of treatment'.
EORTC CAT, European Organisation for the Research and Treatment of Cancer computer adaptive testing; EORTC-QLQ-C30, European Organisation for the Research and Treatment of Cancer Quality of Life Questionnaire Core 30; FACT-G, Functional Assessment of Cancer Therapy-General.

over time will be analysed using mixed models, to allow for the repeated nature of the data by including subject as a repeated effect, and associations across visits (included as a fixed) will be investigated. The baseline score will also be fitted as a fixed effect in all models.

Exploratory endpoints

HRQoL of patients treated with third-line chemotherapy over time will be presented descriptively at each timepoint.

The association between sociodemographic and clinical factors (including age, gender, relationship status, educational level, PS, tumour subtype, site of metastases and baseline laboratory values), financial toxicity and radiological response with global HRQoL, physical, cognitive, social, role, emotional functioning and symptoms at each timepoint will be analysed using univariate mixed models as above. First time-invariant variables (eg, sex, race and age at diagnosis) will be assessed and then time-variant variables to evaluate whether time-specific conditions influence a linear trend of HRQoL over time. Interactions between factors and time will also be explored to assess whether trajectories of HRQoL over time differed by subgroups.

A multivariate model will be constructed as a function of time, sociodemographic and clinical characteristics, and interactions between time and other covariates. Any factors found significant ($p<0.05$) in univariate analysis will be tested in a multivariate mixed-effects models to see if factors of QOL are independent of each other. A backward selection method will be used ($p<0.05$) to identify a parsimonious model.

Patient preference for treatment decision-making, decisional conflict, patient expectations, preference for quantity of life versus QoL, and retrospective views on their decision to receive chemotherapy will be presented descriptively with mean (SD) or median (IQR) at each timepoint as appropriate.

Sample size

For the primary endpoint, the difference from baseline to four cycles will be tested. A mean difference of 10 points in EORTC-QLQ-C30 global HRQoL score is deemed to be clinically relevant with an effect size of 0.3, where the SD of the mean difference is 33.3.[38] With a 90% power and a two-sided 5% significance level, a total of 119 patients are required.[38]To allow for drop outs, an additional 10% of patients will be recruited, giving a total sample size of 132.

We estimate that there will be approximately 30 patients in the third-line chemotherapy cohort within the timeframe of the study.

Missing data

Subjects who have completed online questionnaires will not have any missing data unless they have not completed

the entire questionnaire. The electronic questionnaires have been programmed so that participants are not able to proceed to the next question until all of the questions on the current page have been answered. If patients have not completed the questionnaire, they will be sent an electronic reminder to finish the questionnaire within the time period specified. Regarding paper questionnaires, we will quantify the extent of missing items (ie, number of unanswered questions per patient) and describe these results in our findings. For the EORTC-QLQ-C30, we will follow the EORTC scoring manual guidelines for missing data and use imputation where appropriate.[58] For all other questionnaires, scores cannot be calculated unless the patient has answered all of the items. We will categorise these responses as missing/not answered in the presentation of the results so that 'non-responses' are included in the analysis in order to minimise bias in interpretation.

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