International prospective registry on local treatment approaches in myxoid liposarcomas

Introduction

Standard of care for the majority of intermediate and high grade soft tissue sarcomas (STS) – including myxoid liposarcomas (MLS) –, is surgical resection with radiotherapy, resulting in more favorable local control as compared to surgery alone. With respect to timing, preoperative radiotherapy is associated with fewer late side effects, such as fibrosis, joint stiffness, and edema in comparison to postoperative radiotherapy. However, with an incidence of 35%, wound complications are observed more frequently after preoperative radiotherapy. A shift towards preoperative radiotherapy has been observed in recent years, given the temporary nature of wound complications weighted against the permanent nature of fibrosis, stiffness and edema. However, wound complications, albeit temporary, adversely impact patient quality of life, functional outcome and health care costs.

Myxoid liposarcoma is the most radiosensitive histologic subtypes of soft tissue sarcomas (1-5). During and continuing after radiotherapy until the date of surgery, MLS frequently exhibits a marked tumor volume reduction, in sharp contrast to other subtypes of STS where the volumes as a rule remain fairly constant. In addition, unique to MLS, in 78-100% of the resected specimens ≥50% of pathological response is observed following a standard dose of 50 Gy preoperative radiotherapy delivered using 25 fractions of each 2 Gy. In addition to these remarkable histologic responses, local control following standard preoperative radiotherapy and surgery is exceptionally high, with reported 5-year local control rates of 96-98% in large retrospective series.

The previous phase II DOREMY trial (NCT02106312) was designed to evaluate the oncologic safety and toxicity of a dose reduction of preoperative radiotherapy from 50 Gy to 36 Gy for MLS. The reduced dose did not compromise local tumor control, as no single local recurrence was observed in 79 patients after a median follow up of 25 months. Importantly, the observed 17% wound complication rate and 14% grade ≥2 toxicity are substantially lower as compared to the historical data of the 50Gy dose level (6). Furthermore, the DOREMY evaluated local progression free survival and postponement of systemic therapy in nine patients with 25 oligo-metastatic and/or oligoprogressive MLS lesions following 36Gy of radiotherapy with (n=4) or without (n=21) subsequent surgery (median FU 23 months). The 2-year local

progression free survival rates for definitive radiotherapy and preoperative with resection were 61% and 100%, respectively. For those lesions with local progression, the median interval to local progression was 16 months. Systemic treatment was postponed with a median of 6 months. Although in several studies, the neutrophil-to-leukocyte ratio (NLR) has been shown to be a strong predictor of overall survival in high risk sarcomas (7-12), some reports did not (13, 14). To date, these investigations have not specifically focused on myxoid liposarcomas. This registry may serve as a platform to fill this unmet clinical need.

Given the rarity of the disease, it is practically impossible to conduct a conventional phase III trial to evaluate these local treatment strategies within a reasonable time frame. Several international soft tissue sarcoma centers may consider the results of the phase II DOREMY trial convincing enough to reduce their current standard preoperative radiotherapy dose of MLS to 36Gy (cases for cohort B). On the other hand, there may also be other centers preferring to maintain their preoperative RT dose at 50 Gy (cohort C), waiting for the DOREMY data to mature, or to continue performing surgery first and to apply RT postoperatively to a 60-66Gy dose level (cohort D), or to perform surgery without any radiotherapy (neither pre- nor postoperative, cohort A), or radiotherapy without surgery (cohort E).

In order to expand the body of prospective evidence to optimize local treatment strategy in MLS and the role and dose of RT in it and to assess Patient-Reported Outcome Measures (PROMs) & Health-Related Quality of Life (HRQoL), an international registry study is initiated in the NKI-AVL.

Concise medical information will be collected from medical files and PROMs & HRQoL will be assessed at the following points in time:

- at baseline, prior to the start of first local treatment modality (= T1)

- 3 months after surgery (or after RT in case of definitive RT) (= T2)

- at the end of every follow-up year until 5 years from baseline (= T5)

The study aims to increase the body of prospective evidence regarding the local management of MLS and the role of RT in it. Treatment of study patients in this registry will be identical to the current standard of care in MLS in the participating study center. The additional burden for study patients only consists of completing the questionnaires, which is estimated to be very moderate and as such we propose to designate this project out of legal ethics scope.

Inclusion Criteria

1. Age > 18 years
2. Biopsy proven MLS, including the reciprocal chromosomal translocation t(12;16)(q13;p11)
3. ECOG PS 0-2
4. Written informed consent to share coded information in this international Registry

Patients will be designated to one of the following cohorts:

A. MLS patients managed by surgery only
B. MLS patients receiving preoperative RT to a dose of 36 Gy (equivalent) followed by surgery
C. MLS patients receiving preoperative RT to a dose of 50 Gy (equivalent) followed by surgery
D. MLS patients receiving surgery followed by postoperative RT to a dose of 50-66 Gy (equivalent)
E. MLS patients receiving definitive RT to a dose of 36Gy (equivalent)

Statistical methods

All statistical analyses will be performed using SPSS software.

Missing items in the questionnaire will be handled as follows. If (an) item(s) from a multi-item scale is/are missing, and at least half of the items from the scale have been answered, then scale scores are calculated ignoring any items with missing values, which is the same as assuming that the missing items have values equal to the average of those items. If less than half of the items from the scale have been answered, then the scale score is set to missing. For single-item measures, score is also set to missing.

Descriptive statistics (mean, median, standard deviation, and proportions) will be used to describe the study population, oncological outcome (local recurrence, death), morbidity (wound complications, radiation induced toxicity) and prevalence of HRQoL problems and patient-reported adverse events at each time point. Oncological outcome measures will additionally be analysed by making use of the Kaplan-Meier method.

To investigate factors associated with oncological outcome measures, morbidity, HRQoL, health status and patient-reported adverse events, multivariate linear regression analyses will be carried out.

To assess trajectories of HRQoL, health status and patient-reported adverse events over time, we will carry out repeated analyses using multilevel linear mixed models, which accounts for the intra-patient dependency of the repeated measures. Missing outcomes will be assumed missing at random (MAR). An advantage of multilevel linear mixed models is that all patients can be included in the analyses, regardless of whether they have been missing some follow-up measurements.

Ethical considerations

All participating sarcoma reference centers will apply for local ethical approval for prospective anonymized data collection from their own institutions.

Publication policy

All forthcoming manuscripts and abstracts will be distributed among the participating centers to obtain approval for these prospective data to be presented at scientific meetings and to be published after peer review.

First author will be the researcher performing the analyses and drafting the first version of the manuscript. Second author will be the investigator responsible for the practical execution of the registry: dr. J. Lansu. Last author will be the principal investigator of this study: Prof. dr. R.L.M. Haas.

In between, we will rank the collaborators of the participating centers based on their contributions. If they contributed ≥5% of all patients, 1 co-author position is available per center. For those centers contributing <5% of all patients, these centers will be acknowledged in appropriate paragraphs, but they will not serve as co-author.

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