NEOADJUVANT CHEMOTHERAPY IN HIGH-RISK SOFT TISSUE SARCOMAS: FINAL RESULTS OF A RANDOMIZED TRIAL FROM ITALIAN (ISG), SPANISH (GEIS), FRENCH (FSG), POLISH SARCOMA GROUPS (PSG).

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CONTEXT SUMMARY

Key objective: To investigate whether neoadjuvant histotype-tailored (HT)chemotherapy is superior to standard (S) anthracycline+ifosfamide chemotherapy in 5 high-risk soft tissue sarcoma (STS) subtypes of the extremities or trunk wall.

Knowledge generated: In this randomized multicenter open label 1:1 prospective trial in patients affected by high-risk Myxoid Liposarcoma, Malignant Peripheral Nerve Sheath Tumor, Leiomyosarcoma, Synovial Sarcoma or Undifferentiated Pleomorphic Sarcoma, a non statistically significant difference in 5-yr disease free survival (DFS, 0.55 vs 0.47) and a statistically significant difference in overall survival (OS, 0.76 vs 0.66) in favor of S chemotherapy were observed.

Relevance: HT chemotherapy was not associated with better DFS or OS, suggesting that S chemotherapy should remain the regimen to choose whenever neoadjuvant chemotherapy is used in the 5 histologic subtypes above, accounting for 80% of all high risk STS of the extremities or trunk wall.

ABSTRACT

PURPOSE: To determine whether the administration of histology-tailored (HT) neoadjuvant chemotherapy was superior to the administration of standard anthracycline+ifosfamide (S)neoadjuvant chemotherapy in high-risk soft tissue sarcoma (STS) of extremity or trunk wall.

PATIENTS AND METHODS: This was a randomized open label phase III trial. Patients had localized high-risk STS (grade=3; size $\geq$5 cm) of extremity or trunk wall, belonging to one of the following 5 histologic subtypes: high-grade myxoid liposarcoma (HG-MLPS); leiomyosarcoma (LMS); synovial sarcoma (SS); malignant peripheral nerve sheath tumor (MPNST); undifferentiated pleomorphic sarcoma (UPS). Patients were randomly assigned with a 1:1 ratio to receive 3 cycles of S or HT neoadjuvant chemotherapy. The HT regimens were: trabectedin in HG-MLPS; gemcitabine+dacarbazine in LMS; high-dose prolonged-infusion ifosfamide in SS; etoposide+ifosfamide in MPNST; gemcitabine+docetaxel in UPS. Primary and secondary end-points were disease-free (DFS) and overall survival (OS), estimated using Kaplan-Meier method and compared using Cox models adjusted for treatment and stratification factors. The study is registered at ClinicalTrials.gov, number NCT01710176

Results: Between May 2011 and May 2016287 patients were randomized (97[33.8%] = UPS; 65 [22.6%] = HG-MLPS; 70 [24.4%] = SS; 27 [9.5] = MPNST; 28 [9.7] = LMS). At the final analysis, with a median follow-up of 52 months, the projected DFS and OS probabilities were 0.55 and 0.47 (log-rank p=0.323) and 0.76 and 0.66 (log-rank p=0.018) at 60 months in the S and HT arm, respectively. No treatment-related deaths were observed.

Conclusions and Relevance: In a population of localized, high-risk STS patients HT chemotherapy was not associated with a better DFS or OS, suggesting that S chemotherapy should remain the regimen to choose whenever neoadjuvant chemotherapy is used in high-risk STS.

Key words:

Sarcoma, localized, neoadjuvant chemotherapy, radiotherapy, randomized trial, prognosis, survival

Introduction

Despite optimal local treatment, 50% of patients affected by localized high-risk soft tissue sarcoma (STS) of the extremities or trunk wall die of metastatic disease[1,2]. Neoadjuvant/adjuvant chemotherapy has been tested in several trials and 2 meta-analyses[3,4], showing a 5-10% overall survival (OS) benefit. However these studies and meta-analyses have been weakened by conflicting results of individual trials[5].

The Italian Sarcoma Group (ISG) studies were characterized by the selection of patients marked by a higher risk (tumors $\geq$5 cm and malignancy grade of 3). The first study[6,7] reported a benefit in OS and DFS following a treatment with5 courses with anthracycline+ifosfamide adjuvant chemotherapy vs no further treatment. However a drop in dose intensity was observed after the administration of 3 cycles. A second study in collaboration with the Spanish Sarcoma Group (GEIS) showed that the administration of 3 courses of the same anthracycline+ifosfamide chemotherapy in the neoadjuvant setting was not inferior to the administration of 5[8].

In collaboration with GEIS, the French Sarcoma Group (FSG) and the Polish Sarcoma Group (PSG) we then compared the administration of standard (S) anthracycline+ifosfamide vs a histotype-tailored (HT) neoadjuvant chemotherapy in 5 major STS histologic subtypes, selected as in the metastatic setting they had demonstrated specific sensitivities to drugs different from anthracycline[9-13].

This study was terminated slightly early, following the 3rd pre-specified futility analysis and after the inclusion of 287/350 patients, for the observation at a median FU of 1 yr of a HR of 2.0 in DFS and 2.7 in OS of the HT approach[14]. We report herein the final results.

Patients and Methods

Study Design

This is a prospective, open label, randomized, controlled study comparing S with HT neoadjuvant chemotherapy for patients with primary localized high-risk STS. Patients were enrolled in 32 hospitals in one of the following 4 countries: Italy, Spain, France and Poland.

The trial protocol and all amendments were approved by the appropriate independent ethics committee at each trial center. The trial was conducted in accordance with the provisions of the Declaration of Helsinki. All patients provided written informed consent before enrollment. The full protocol is available in the **Appendix**.

Participants

Patients were eligible if aged 18 years or older; had a histologically proven and centrally reviewed (before randomization) diagnosis of localized STS, originating in an extremity or trunk wall, belonging to high-grade myxoid liposarcoma (cellular component > 5%, HG-MLPS), leiomyosarcoma (LMS), synovial sarcoma (SS), malignant peripheral nerve sheath tumor (MPNST) or undifferentiated pleomorphic sarcoma(UPS); with high malignancy grade (grade 3 according to FNCLCC grading system[15]), ≥5 cm in longest diameter at baseline radiological assessment.

Patients were ineligible if they had distant metastases.

Other inclusion and exclusion criteria can be found in the **Appendix.**

Randomization and blinding

Patients were randomly assigned, with a 1:1 ratio, to receive 3 cycles of neoadjuvant S or HT chemotherapy.

Randomization was done centrally at the clinical trial center in Genova, stratified by administration of preoperative RT versus no preoperative RT and by country of enrollment (Spain vs France vs Poland vs Italy) and was not balanced by histotype or participating site. Computer-generated random lists were prepared using permuted balanced blocks of size 4 and 6 in random sequence. An internet-based randomization system ensured concealment of the treatment assignment until the patient had been registered into the system. Treatment allocation was communicated electronically to the study center and by the local investigator to the patient.

No blinding of treatment assignments was deemed possible, due to obvious differences in schedules and modes of administration as well as in toxicity across regimens.

Procedures

In S arm, chemotherapy had to be repeated every 21 days and included epirubicin 60 mg/m2/day, short infusion, days 1 and 2 + ifosfamide 3g/m2/day, days 1, 2, 3.

In HT arm, for HG-MLPS chemotherapy had to be repeated every 21 days and consisted of trabectedin 1.3 mg/m2, given in 24-hour continuous infusion. Of note, at the time of the start of the study trabectedin was not yet available and 3 patients received as a tailored regimen adriamycin 75 mg/m2/day monotherapy, short infusion every 3 weeks. Trabectedin was then introduced with the first amendment (November 2011); for LMS chemotherapy had to be repeated every 14 days and consisted of gemcitabine 1800 mg/m2 on day 1 intravenously over 180 min and dacarbazine 500 mg/m2 on day 1 intravenously over 20 min; for SS chemotherapy consisted of high-dose ifosfamide 14 g/m2, given in 14 days by means of an external infusion pump, every 28 days; for MPNST chemotherapy had to be repeated every 21 days and consisted of etoposide 150 mg/m2/day, days 1, 2, 3 and ifosfamide 3g/m2/day, days 1, 2, 3; for UPS chemotherapy had to be repeated every 21 days and consisted of

gemcitabine 900 mg/m2 on days 1 and 8 intravenously over 90 min and docetaxel 75 mg/m2 on day 8 intravenously over 1 h.

Toxic effects were graded using the National Cancer Institute Common Toxicity criteria, version 4.0.

Dose reductions were foreseen and reported in the **Appendix**

Response according to RECIST 1.1[16] and modified Choi criteria[17-19] was assessed after the 1st cycle and after the third cycle at the time of surgery.

Surgery was planned 3 to 4 weeks after the administration of last preoperative cycle and not before 4 weeks from the end of preoperative RT.

Follow-up was carried out every four months for the first 2 years after the end of treatment, then 6 monthly from the 3rd to the 5th year after the end of treatment and yearly after the 6th year.

Statistical Analysis

The Kaplan–Meier method[20] was used to estimate DFS and OS. For the analysis of DFS, progressions before surgery, relapses after surgery and death without progression or relapse were considered as events, while patients who were alive and disease-free or who were lost to follow-up were censored at the time of the last examination. For the analysis of OS, data for patients who were alive or who were lost to follow-up were censored at the time of the last contact. Between-group differences in DFS and OS were assessed with the use of a stratified log-rank test. Hazard ratios and associated 95% confidence intervals (CI) were assessed with the use of a stratified Cox proportional-hazards model[21]. All randomized patients were included in DFS and OS analyses and considered in the treatment group assigned at randomization (the intention-to-treat (ITT) population).

SAS version 9.2 and IBM SPSS version 22.0 were used.

The original Sample Size estimates were based on the consideration that the HT approach could have been associated, overall, with a 1/3 reduction in the hazard of relapse (HR=0.667), corresponding to a reduction in the long term risk of relapse from 40% to 27%. In order to assess such an effect with 80% power at the 5% (1-sided) significance level, 150 events (relapses or deaths) had to be observed over 350 patients randomized. The final analysis had been planned after the observation of the 150th event, expected to occur 4-5 years after the start of the study.

Yearly interim futility analyses were performed to assess whether the study hypothesis that HT was associated with a 1/3 reduction in the hazard of relapse was still viable[22],while no interim analysis aimed at stopping the study for efficacy was planned or conducted. Therefore, no correction for multiple analyses (alfa spending) was needed, since the alfa error was entirely preserved for the final analysis.

An external independent data monitoring committee (IDMC) oversaw the trial and assessed the safety and efficacy at pre-specified interim analyses. Committee members are listed in the **Appendix**.

On May 23rd 2016 the IDMC recommended the early termination of the study on the basis of the 3rd pre-specified futility interim analysis, showing at a median follow-up of 1 yr an HR of 2 in DFS of the HT approach. This was also associated to an HR of 2.7 in OS. These results were reported in full, as recommended by the IDMC[14]. The final study analysis was maintained, as planned, 2 yrs later, but an amendment was introduced, and the one-sided test was replaced by a 2-sided test (still at the 5% alfa level), based on the results of the futility analysis, which suggested a higher risk in the HT arm. The final analysis was therefore planned after the observation of 130 events, allowing an 80% power to confirm at the 5% 2-sided level the significant difference observed at the 3rd futility analysis.

As a consequence, caution adopted in the interpretation of the interim analysis should be applied also to the present one, since early study results were used to modify the null-hypothesis which is being tested.

Ancillary analysis

Based on the 10-year OS predicted by the nomogram included in the Sarculator validated tool[23](available at http://www.sarculator.com),patients were categorized into 2 groups: those with a 10-year predicted OS < 60% and ≥ 60%. The Kaplan–Meier method was used to estimate DFS and OS for patients allocated to each category of Sarculator's predicted 10-year OS. Between-group differences were assessed on the ITT population by using a stratified log-rank test. HR and 95%CI were calculated with a stratified Cox proportional-hazards model as described above.

Results

From May 2011 to May 2016, 435 patients were registered and 287 were randomized (145 in S arm and 142 inHT arm); 177 were males and 110 females (**Table 1**). The ITT population is depicted in **Figure 1**.

Two-hundred and eighty-one [97.9%] of 287 patients were operated, while 6 (3 [2.1%] of 145 patients in S arm and 3 [2.1%]of 142 patients in HT arm) were not, for locally advanced disease (2 cases, 1 per study arm), occurrence of distant metastases in the preoperative phase (3 cases, 2 in S arm and 1 in HT arm) and 1 refusal (1 in HT arm).

At the final analysis, with a median follow-up of 52 months (range 22-88; IQ28), 132 events were observed, 63 in S arm and 69 in HT arm.The corresponding DFS probabilities at 60 months were 0.55 (95%CI: 0.46,0.63) in Arm A and 0.47 (95%CI: 0.38,0.57) in Arm B (**Figure 2A**). The HR, estimated in a stratified Cox's proportional Hazards model, was 1.23 (95%CI 0.88,1.73; p=0.32). A per protocol analysis, excluding ineligible patients, was consistent: HR 1.23 (95%CI: 0.86-1.74).

Seventy-three deaths were observed, 28 in S arm and 45in HT arm. The corresponding OS probabilities at 60 months were 0.76 (95%CI: 0.67,0.84) in S armand 0.66 (95%CI: 0.57,0.75) in HT arm (**Figure 2B**). The HR, estimated in a univariate Cox's proportional Hazards model, was 1.77 (95%CI 1.10,2.83; p=0.02). A per protocol analysis, excluding ineligible patients, was consistent: HR 1.69 (95%CI: 1.05 -2.72).

Two hundreds and forty [83.6%] of 287 patients had measurable disease at the time of study entry and were evaluable for RECIST 1.1, 121[83.4%] of 145 patients in S arm and 119 [83.8%] of 142 patients in HT arm, while 47[16.4%] of 287 (24[16.5%] of 145 patients in S arm and 23[16.2%] of 142 patients in HT arm) were included in the study without measurable disease, after prior excision.
Of the 240 patients evaluable for response 230 [96%], 117/121[96.6%] in S arm and 113/119 [94.9%] in HT arm, were assessed by local investigator. No complete responses were observed. Twenty-three [10%] of 230 patients obtained a partial response (16 [13.6%] of 117 patients in S arm and 7 [6.1%] of 113 patients in HT arm), while 184 [80%] of 230 patients had stable disease (93 [79.4%] of 117 patients in S arm and 91 [80.5%] of 113 patients in HT arm). Twenty-three [10%] of 230 patients (8 [6.8%] of 117 patients in S arm and 15 [13.2%] of 113 patients in HT arm) had progressive disease. An analysis on centralized review of response and outcome will be the subject of a separate report.

No toxic deaths were observed in either study arm. Safety and toxicity are reported in details in the supplement.

Ancillary analysis

Patients with a sarculator predicted OS≥ 60% had a DFS and OS at 5 year of 0.61 and 0.81 in the S and 0.60 and 0.75 in the HT arm respectively (DFS HR: 1.01; 95%CI 0.61,1.67; p=0.96; OS HR: 1.51; 95%CI

0.75,3.05; p=0.25. **Figure 3A-B**). Patients with a predicted OS<60% had a DFS and OS at 5 yr of 0.45 and 0.66 in the S and 0.34 and 0.55 in the HT arm respectively (DFS HR: 1.47; 95%CI 0.92,2.37; p=0.11; OS HR: 1.91; 95%CI 1.00,3.66; p=0.05. **Figure 3C-D**).

Discussion

This phase III trial in patients with localized high-risk STS of the extremities and trunk wall failed to show a superior DFS, primary study end-point, of HT over S neoadjuvant chemotherapy. On the contrary, there was a trend in favor of S chemotherapy, which was consistent with a parallel OS difference..

Of note, the difference in DFS in favor of S chemotherapy was statistically significant at the 3rd futility analysis, but its magnitude decreased at this final analysis. Indeed, the HT group initially seemed to reproduce the no-treatment group of the first ISG trial[14]: its projected 4-yr DFS at the time of the 3rd futility analysis was 0.38, while the 4-yr DFS of the no-treatment arm of the first ISG trial was 0.37[6]. At the end, the HT chemotherapy group performed better than initially detected (5 yr DFS 0.47), suggesting some effect of the HT chemotherapy per se and this affected the advantage in DFS more than the advantage in OS in favor of S chemotherapy at this final analysis. Thus, this trial cannot be interpreted as a formal proof that neoadjuvant chemotherapy is effective as such. Furthermore, the trial was originally designed with a 1-sided superiority test, meaning that the alternative hypothesis of superiority of the S arm was not contemplated. Since the switch to the 2-sided test was dictated by the results of the interim analysis, caution is needed in the interpretation of hypothesis testing. However, various considerations, including the consistency of the differences in the various analyses and the coherence between the DFS and OS figures reported in our and in other similar studies[5-7], support the validity of our findings.

Of note randomization was not stratified by histologic subtype. As a result, as shown in Table 1, the distribution of subtypes was not balanced between the two study arms, with sizably more HG-MLPS and fewer UPS in the S arm, which may partially explain the observed differences in the survival outcome.

However it is worth noting that the DFS and OS figures of S chemotherapy in the three ISG subsequent trials were superimposable: DFS were 0.50[6,7], 0.57[8] and 0.55 and OS were 0.69[6,7], 0.70[8] and 0.76 at 5-yr respectively, suggesting that these are the figures that new treatment modalities/agents will have to compare with, provided the study population is truly high-risk.

Recently, the largest and negative adjuvant trial[24] (EORTC-62931) was revisited. Patients were stratified by the predicted OS, using a validated nomogram[23]. This analysis[25] showed how the study population was marked by a median predicted OS greater than70%. When a cut-off of 60% was used, patients with a predicted OS inferior to 60% had a significant benefit in DFS and OS by the administration of adjuvant chemotherapy.

Similarly a non-pre-specified, subgroup analysis using the same predictive nomogram[23]to stratify baseline risk of patients enrolled into this trial suggested that the benefit in favor of S chemotherapy may be higher when the baseline risk is higher. Interestingly, the proportional (not only the absolute) risk reduction of the administration of chemotherapy looks lower when the baseline risk is lower[1]. One may hypothesize that adjuvant or neoadjuvant chemotherapy should be reserved to STS patients with a high baseline risk (a cutoff of 40% risk was selected). Clearly, a higher risk corresponds on average to a higher malignancy grade and thus, potentially, to a higher efficacy of chemotherapy.

In this trial, radiotherapy (RT) was predominantly carried out post-operatively. In the previous trial, it was done pre-operatively in more than one half of patients[8]. Assuming free surgical margins as an indicator, their proportion was higher in the previous trial and lower in the latter (R0 resections were obtained in 90% of the patients in the previous trial against 80% in this latter one). We previously

showed that the preoperative combination of S chemotherapy with RT is feasible[26] and apparently offsets the adverse impact of positive surgical margins[27]. In the end, one should not overlook the local impact of pre-operative treatments. In other words, while the primary aim of neoadjuvant chemotherapy in operable patients is systemic, a local benefit is likely to occur at least in a proportion of patients. Function preservation may well be part of this benefit.

In this trial, we conceived HT regimens without anthracyclines. In the end, this trial shows that anthracyclines are still an important component of chemotherapy of STS in the eligible histologic subtypes. Even for this reason, we would not conclude that “any” HT was proven to be inferior, since HT regimens could have well included an anthracycline. As a matter of fact, HT is widely used in the advanced setting of STS and in a subgroup such as LMS probably the “best” regimen might combine an anthracycline with dacarbazine[28].

In addition, after the third futility analysis, a decision to continue recruitment in the cohort of MLPS was made, to test the hypothesis of a possible equivalence between trabectedin and S chemotherapy. Trabectedin has recently been proven to be combinable to RT[29] and this could well become an alternative to anthracycline-based chemo in HG MLPS. Recruitment of the expansion of this cohort will be completed in June 2020.

In conclusion, current clinical practice guidelines state that adjuvant/neoadjuvant chemotherapy in adult patients with high-risk localized STS is not standard practice, but it is an option to propose in conditions of uncertainty for shared decision-making. With all the caveats discussed above, we believe that the data provided in the final analysis of this trial may support the choice of an anthracycline-based neoadjuvant chemotherapy whenever an adjuvant treatment is considered and the risk of relapse is high.

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Table 1. Clinical and pathological characteristics of patients randomized by treatment arm (ITT population).

	Treatment		
	Standard chemotherapy (No.=145)	Histotype tailored chemotherapy (No.=142)	All (No.=287)
Age [years, mean (SD)]	*48 (13)*	*49 (13)*	*40 (13)*
IQ range	*20*	*21*	*20*
Gender			
Male	*92(63.45%)*	*85(59.86%)*	*177(61.67%)*
Female	*53(36.55%)*	*57(40.14%)*	*110(38.33%)*
Size [mm, mean (SD)];	*112 (51)*	*105 (65)*	*109 (58)*
MIN-MAX	*26-360*	*10-680*	*10-680*
IQ range	*52.00*	*60.00*	*55.00*
Histology			
High-grade Myxoidliposarcoma	*37 (25.52%)*	*28 (19.72%)*	*65 (22.65%)*
Synovial sarcoma	*36 (24.83%)*	*34 (23.94%)*	*70 (24.39%)*
Malignant peripheral nerve sheath tumor	*15 (10.34%)*	*12 (8.45%)*	*27 (9.41%)*
Leiomyosarcoma	*12 (8.28%)*	*16 (11.27%)*	*28 (9.76%)*
Undifferentiated pleomorphic sarcoma	*43 (29.66%)*	*50 (35.21%)*	*93 (32.40%)*
*Mixofibrosarcoma**	*0 (0.00%)*	*2 (1.41%)*	*2 (0.70%)*
*Unclassified spindle cell**	*1 (0.69%)*	*0 (0.00%)*	*1 (0.35%)*
*Pleomorphic liposarcoma**	*1 (0.69%)*	*0 (0.00%)*	*1 (0.35%)*
Site			
Thoracic wall	*5(3.45%)*	*4 (2.82%)*	*9 (3.14%)*
Abdominal wall	*2 (1.38%)*	*2 (1.41%)*	*4 (1.39%)*
Paravertebral	*4 (2.76%)*	*1 (0.70%)*	*5 (1.74%)*
Shoulder girdle	*15 (10.34%)*	*8 (5.63%)*	*23 (8.01%)*
Upper limb	*9 (6.21%)*	*11 (7.75%)*	*20 (6.97%)*
Pelvic girdle	*10 (6.90%)*	*18 (12.68%)*	*28 (9.76%)*
Lower limb	*100(68.97%)*	*98 (69.01%)*	*198 (68.99%)*
RT			
Pre-operative RT done	*17(11.72%)*	*18(12.68%)*	*35(12.20%)*
Post-operative RT done	*96(66.21%)*	*95(66.90%)*	*191(66.55%)*
Pre and Post-operative RT done	*2(1.38%)*	*1(0.70%)*	*3(1.05%)*
RT not done	*30(20.69%)*	*28(19.72%)*	*58(20.21%)*
*Microscopic Surgical Margins **			
R0	*111(78.16%)*	*113(81.29%)*	*224(79.71%)*
R1	*29(20.42%)*	*21(15.10%)*	*50(17.79%)*
R2	*2 (1.42%)*	*4 (2.87%)*	*6 (2.13%)*
Unknown	*0*	*1 (0.74%)*	*1 (0.37%)*
*Type of surgery****			
Conservative	*104(92.04%)*	*105(95.45%)*	*209(93.76%)*
Amputation	*9(7.96%)*	*5(4.45%)*	*14(6.28%)*

* Ineligible histology at study entry; **6 patients were not operated (3 [2.1%] of 145 patients in S arm and 3 [2.1%] of 142 patients in HT arm) for locally advanced disease (2 cases, 1 per study arm), occurrence of distant

metastases in the preoperative phase (3 cases, 2 in S arm and 1 in HT arm) and 1 refusal (1 in HT arm);
***excluding abdominal wall, thoracic wall and paraspinal

Declaration of Interests

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Figure legends

Figure 1: Consort Diagram

Figure 2: Disease-Free Survival (panel A) and Overall Survival (panel B) of standard versus histotype-tailored chemotherapy;

Figure 3: Disease-Free Survival (panel A) and Overall Survival (panel B) of standard versus histotype-tailored chemotherapy in patients with Sarculator predicted OS > 60%; Disease-Free Survival (panel C) and Overall Survival (panel D) of standard versus histotype-tailored chemotherapy in patients with Sarculator predicted OS < 60%