Outcomes of elderly advanced soft tissue sarcoma patients treated with first-line chemotherapy: a pooled analysis of twelve EORTC Soft Tissue and Bone Sarcoma Group trials.

Running Title: Elderly outcomes in EORTC-STBSG chemotherapy trials.

Younger E[1], Litière S[2], Le Cesne A[3], Mir O[3], Gelderblom H[4], Italiano A[5], Marreaud S[2], Jones RL[1], Gronchi A[6], van der Graaf WT[1,7,8]

Affiliations :

1. The Royal Marsden NHS Foundation Trust, London, U.K.
2. EORTC Headquarters, Brussels, Belgium
3. Gustave Roussy Institute, Villejuif, France.
4. Leiden University Medial Center, The Netherlands.
5. Institut Bergonié, 33076 Bordeaux, France.
6. Fondazione IRCCS Istituto Nazionale dei Tumori, Milano, Italy.
7. The Institute of Cancer Research, London, U.K.
8. Radboud University Medical Center Nijmegen, The Netherlands

Corresponding Author
Professor Winette van der Graaf MD PhD
The Institute of Cancer Research
15 Cotswold Road
Sutton, Surrey
United Kingdom
Tel: 0208-722-4448
Fax: 0207-349-0701
Email: winette.vandergraaf@icr.ac.uk

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Abstract

Background

Almost half of patients diagnosed with soft tissue sarcoma (STS) are older than 65 years, however the outcomes of elderly patients with metastatic disease are not well-described.

Patients and Methods

An elderly cohort of patients aged ≥65 years was extracted from the EORTC-STBSG database of patients treated with first-line chemotherapy for advanced STS within twelve EORTC clinical trials. End points were overall survival (OS), progression free survival (PFS) and response rate (RR).

Results

Of 2810 participants in EORTC trials, there were 348 elderly patients (12.4%, median 68 years; IQR 67-70; max.84 years) and 2462 patients aged <65 years (median 49 years; IQR 39-57). Most elderly patients had performance status of 0 (n=134; 39%) or 1 (n=177; 51%). Leiomyosarcoma (n=130; 37%) was the most common histological subtype. Lung metastases were present in 181 patients (52%) and liver metastases in 63 patients (18%). Overall, 126 patients (36%) received Doxorubicin, 114 patients (33%) Doxorubicin-Ifosfamide, 43 patients (12%) Epirubicin, 39 patients (11%) Trabectedin and 26 patients (7%) Ifosfamide. Overall RR was 14.9% (n=52), median PFS 3.5 months (95% CI 2.7-4.3) and median OS 10.8 months (95%CI 9.43-11.83). In patients <65 years overall RR was 20.3% (n=501), median OS 12.3 months (95%CI 11.9-12.9) and median PFS 4.3 months (95%CI 3.9-4.6).

Conclusion

Elderly metastatic STS patients treated with first-line chemotherapy were largely underrepresented in these EORTC STS trials. Their outcomes were only slightly worse than younger patients. Novel trials with broader eligibility criteria are needed for elderly patients. These should incorporate geriatric assessments and measurements of age-adjusted health-related quality of life.

Introduction

Global life expectancy is increasing annually. In 2015, the World Health Organisation (WHO) estimated that this figure reached 71.4 years, exceeding 82 years in twelve countries.(1) Cancer is predominantly a disease of the elderly due to the cumulative acquisition of genetic abnormalities and lifetime exposure to carcinogens.(2) Currently more than 60% of all cancer diagnoses and 70% of cancer-related deaths occur in patients aged >65 years.(3) In view of the ageing population, it is widely acknowledged that the incidence of cancer will continue to rise significantly in the years to come.(3) The challenges of treating elderly cancer patients are multifactorial. Physiological changes associated with ageing, comorbid medical conditions, psychosocial factors, functional and nutritional status and polypharmacy are several key issues which require careful consideration in elderly cancer patients.(4) The interaction of these factors is complex, and their influence on cancer biology, treatment tolerance, compliance, efficacy and outcomes remains uncertain.(3) Currently a multidisciplinary approach is recommended, however it is undeniable that new guidelines specifically for elderly cancer patients are urgently needed.(2)

Despite the large number of elderly patients with cancer, they are often disproportionally underrepresented in clinical research trials.(5) Strict exclusion criteria, attrition (mortality, relocation), patient heterogeneity, costs and longer recruitment processes contribute to this finding.(6) Data from studies in younger patients are often extrapolated in order to aid clinical decision-making in elderly patients. Outcomes for elderly patients in clinical trials are not routinely distinguished from all data, thus limiting evidence-based decision-making in clinical practice. Furthermore, dose reductions are frequently implemented in elderly 'frail' patients, without clear evidence of treatment efficacy at lower dose levels.(3)

Soft tissue sarcomas (STS) are rare, heterogeneous tumors which account for approximately 1% of all adult solid malignancies.(7) Approximately half of patients with localised, intermediate or high grade tumours will eventually develop metastatic disease.(8) Cytotoxic chemotherapy, usually an

anthracycline-based regimen, has been the mainstay of treatment since the 1970s.(9) Median overall survival for patients with advanced soft tissue sarcoma is around 12-19 months.(10-13) STS are common in elderly patients aged ≥65+ years, with an age-adjusted incidence of 11.3 cases per 100,000 population compared with 2.3 cases per 100,000 in those aged <65 years (SEER database).(14) Although approximately 40-50% of all patients diagnosed with STS are aged >65 years, the median age of patients in prospective first-line chemotherapy trials for advanced STS ranges from 48-60 years.(14-17) The objective of this study is to examine outcomes of elderly patients treated with first-line chemotherapy within EORTC-STBSG clinical trials.

Patients and Methods

Patient sample

The EORTC-STBSG database comprises 3711 patients treated with first-line chemotherapy in 15 EORTC advanced soft tissue sarcomas trials. In this analysis, patients with GIST, those who had received prior (adjuvant or palliative) chemotherapy and patients for whom age or time to treatment failure (discontinuation of treatment for any reason, including disease progression, toxicity or death) was missing are excluded. Furthermore, we wished to focus on outcomes with currently used chemotherapy schedules and consequently patients treated with CYVADIC, Ifosfamide 12mg/m^2, or Brostallicin were not included in this analysis. Therefore, 2810 patients from 13 trials were used for the descriptive part of this report. Elderly patients were defined as those aged 65 years or greater. The randomised trial of doxorubicin versus doxorubicin plus ifosfamide (EORTC 62012) had an upper age range of 60 years (oldest patient 63 years), and therefore patients in this trial did not contribute to the elderly subgroup. From the remaining twelve studies 348 elderly patients were identified (Appendix: Summary of EORTC-STBSG clinical trials in this analysis and elderly patients per protocol). Ethical approval was not required for this analysis.

End points

End points for this analysis were overall survival, progression free survival and response to chemotherapy. Progression free survival (PFS*)* was defined as the time interval between the date of randomisation, or the date of prospective registration in the nonrandomised trials, and the date of first report of progression or death whichever came first. Patients who were alive and without progressive disease at the last follow up date were censored. Overall survival (OS) was computed from the date of randomisation (in randomised trials) or the date of prospective registration (in nonrandomised trials) to the date of death. Patients who were alive at the last follow up date were censored. Response to chemotherapy was evaluated in all trials using WHO response criteria or RECIST; complete reponse, partial reseponse, stable disease or progressive disease.

Covariates

The variables included in the study were demographic data, histological subytpe of sarcoma and the extent of the disease at the time of inclusion in the trials and the assigned treatment. The demographic variables include age and performance status before the start of chemotherapy. Performance status (PS) was measured on the WHO scale (except for two trials in which it was retrospectively converted from Karnosky scale to the WHO scale). As few patients had PS 3, PS 2 and 3 were combined in the same category named "PS 2+". Variables related to the history of sarcoma were prior radiotherapy, and prior surgery which had three categories i.e. no surgery, partial surgery (includes palliative surgery and other) and total surgery. Note that for the study 62012, data about primary surgery was not collected, therefore the variable was missing for all the patients of that trial. Histopathological grade estimated by a panel of reference pathologists was preferred over the use of local diagnosis to ensure the consistency and homogeneity of the database. Similarly the reviewed histopathological cell type was preferred over the local diagnosis.

The treatment was aggregated in 5 categories: (liposomal) doxorubicin alone (doxorubicin 75mg/m^2, caelyx 35mg/m^2), epirubicin (epirubicin 75mg/m^2, epirubicin 50mg/m^2 [days 1-3], epirubicin

150mg/m^2), ifosfamide alone (ifosfamide 5 mg/m^2, ifosfamide 3mg/ m^2 [days 1-3], ifosfamide 9 mg/m^2 [continuous infusion over 72 hours]), the combination of doxorubicin and ifosfamide (doxorubicin 50mg/m^2 - ifosfamide 5 mg/m^2, doxorubicin 75 mg/m^2 - ifosfamide 5 mg/m^2, doxorubicin 75 mg/m^2 - ifosfamide 10 mg/m^2) and trabectedin (1.3 mg/m², 3 hrs infusion or 1.5 mg/m², 24 hrs infusion).

Statistical methodology

All baseline variables are described. The categorical data are summarized by frequencies and percentages, and the continuous covariates are summarized by median, interquartile range and the overall range. The overall and progression free survival were estimated by the Kaplan–Meier method. Medians are provided with corresponding 95% Confidence Intervals (CI). Response to chemotherapy is summarized as a percentage with corresponding 95% CI.

Results

A total of 348 elderly patients with advanced soft tissue sarcoma who entered in EORTC first-line chemotherapy clinical trials between 1980 and 2012 were identified for this analysis.

Patient Characteristics (Table 1)

The median age of elderly patients was 68 years (IQR 67-71), with a maximum of 84 years. Most patients had a performance status (PS) of 0 (n=134, 38.5%) or 1 (n=177, 50.9%). A small number of patients had a PS of 2+ (n=32, 9.2%). Histopathological grade was most commonly grade III (n=89, 25.6%) or grade II (n= 71, 20.4%), however, data regarding tumour grade were 'missing' for almost half of patients (n=155, 44.5%). The most frequent histological subtypes were leiomyosarcoma (n=130, 37.4%), malignant fibrous histiocytoma or undifferentiated pleomorphic sarcoma (MFH/UPS) (n=55, 15.8%) and liposarcoma (n=30, 8.6%). Of note, MFH is no longer part of the currently used nomenclature and has been reclassified as UPS. There were 43 patients (12.3%) with unclassified or missing histological subtype. Overall, 167 patients (48%) had involvement of the

primary site of disease, more than half of patients had pulmonary metastases (n=181, 52.0%), 63 patients (18.1%) had liver metastases, 24 patients (6.9%) bone metastases and 139 patients (39.9%) with metastases at 'other' sites.

Prior surgical details were missing for more than half of patients (n=194, 55.7%), however, of the remaining 154 patients with available data, 65 patients had received previous partial surgery, and 69 patients previous total surgery. Prior radiotherapy details were missing for 76 patients (21.8%), however, out of the remaining 272 patients, 71 patients (26%) had received prior radiotherapy. Overall, 126 (36%) patients were treated with first-line single-agent doxorubicin, 114 pts (33%) with combination doxorubicin and ifosfamide, 43 pts (12%) with epirubicin, 39 pts (11%) with trabectedin and 26 (7%) with single-agent ifosfamide.

Outcomes

The median follow-up time for elderly patients who were still alive at the time of their analyses was 9.5 months (IQR 6-25). Of note, the median follow-up time for patients treated with trabectedin who were still alive at the time of the clinical cut-off date was considerably shorter than for the other treatment groups (trabectedin 6.7 months (IQR 5.8-9.2) vs doxorubicin+ifosfamide 24 months (IQR 7-38), doxorubicin alone 14 months (IQR 5.5-29), epirubicin 24 months (IQR 8-43) and ifosfamide alone 4 months (IQR 3.5-16)). At the time of their respective analyses, 84 patients (24.1%) were alive and 264 patients (75.9%) were deceased.

Response Rates (Table 2)

In total, 48 patients (13.8%) had a partial response and 4 patients (1.1%) had complete response. There were 127 patients (36.5%) with stable disease and 115 patients (33.0%) with progressive disease as best response. Response was not evaluable for 49 patients (14.1%). Radiological responses were primarily seen in patients treated with single-agent doxorubicin (n=22) or combination doxorubicin plus ifosfamide (n=21).

Overall Survival (OS) (Table 3)

Median OS was 10.8 months (95% CI 9.4-11.8); for single agent doxorubicin 9.8 months (95% CI 7.4-11.5), and doxorubicin plus ifosfamide 12.1 months (95% CI 9.6-14.9), epirubicin 9.9 months (95% CI 5.9-11.8), single-agent ifosfamide 9.7 months (95% CI 2.9-14.4), trabectedin 17.3 months (95% CI 9.4-17.3). Due to the shorter follow-up in the trabectedin group there is some overestimation of overall survival in this group as compared to the other treatment groups. Median OS across treatment groups at 3, 6 and 12 months respectively were 82.6%, 69.2% and 44.0%. Kaplan-Meier OS curves for all patients and according to treatment received are available as supplementary material.

Progression Free Survival (PFS) (Table 4)

Median PFS was 3.48 months (95% CI 2.76-4.27); doxorubicin 3.1 months (95% CI 2.1-4.1), doxorubicin plus ifosfamide 5.2 months (95% CI 3.1-6.4), epirubicin 3.8 months (95% CI 1.4-6.2), ifosfamide alone 2.2 months (95% CI 1.4-3.8), trabectedin 2.8 months (95% CI 1.6 – 5.8).

Older, elderly patients (aged ≥75 years)

There were 31 patients aged ≥75 years. Their median survival was 10.1 months (95% CI 4.8-13.0) and median PFS was 3.4 months (95% CI 1.4 – 5.5).

Comparison of elderly (≥65 years)) versus younger patients (<65 years) (Tables 5,6,7))

There were 2462 patients aged <65 years, who were treated in thirteen EORTC-STBSG trials of the same chemotherapy regimens described above. The median age of these patients was 49 years (IQR 39-57). Median follow-up was 46 months (IQR 29-72).

Patient characteristics are summarised in Table 1. In patients aged <65 years a higher proportion were PS 0 compared with elderly patients (45.6% vs 38.5%), however, in both age groups the majority of patients were either PS 0 or 1 (91.4% younger vs 89.4% elderly). In patients aged <65 years, tumours

were most commonly histopathological grade 3 (34.2%) or grade 2 (28.6%), however tumour grading was missing for 705 patients (28.6%). As observed in elderly patients, the most common histological cell type in patients aged <65 years was leiomyosarcoma (n=741, 30.1%). The second most frequent histological subtype in younger patients was synovial sarcoma (n=254, 10.3%); only reported in 11 elderly patients (3.2%). MFH (UPS) was proportionally less common in patients aged <65 years compared with the elderly patient group (9.7% vs 15.8%). The frequency of liposarcoma was similar in both age groups (9.8% vs 8.5%).

The lung was the most common site of metastases in patients aged <65 years (57.6%). Liver metastases were present with similar frequency in younger and elderly patients (17.1% vs 18.1%). A slightly higher proportion of younger patients had bone metastases compared with elderly patients (10.2% vs 6.9%). Rates of prior partial surgery (19.3%) and total surgery (19.6%) in younger patients were almost identical to elderly patients. As seen in the elderly patient group, very few patients had received prior radiotherapy; 20.4% younger vs 26.5% elderly patients.

Treatments received by patients aged <65 years (younger) are compared with treatments received by elderly patients; doxorubicin (36% younger vs 36% elderly), doxorubicin plus ifosfamide (40% younger vs 33% elderly), epirubicin (11% younger vs 12% elderly), ifosfamide alone (11% younger vs 7% elderly), trabectedin (2% younger vs 11% elderly).

In patients aged <65 years, 424 patients (17.2%) achieved a partial response and 77 patients (3.1%) a complete response. There were 974 patients (39.6%) with stable disease, 784 patients (31.8%) with progressive disease and 203 patients (8%) for whom disease was not evaluable. Therefore, in comparison with elderly patients, younger patients (<65 years) had a slightly higher radiological response rates (20.3% vs 14.9%). Radiological responses in younger patients were primarily seen in

those treated with combination doxorubicin plus ifosfamide (n=227, 23.0%). Table 5 summarises radiological responses in younger versus older patients according to treatment received.

Median overall survival (OS) was better in younger patients (<65 years) compared with elderly patients (>65 years); median OS 12.3 months (95% CI 11.9 – 12.9) vs median OS of 10.8 months (95% CI 9.4-11.8) in elderly patients (Table 6). Younger patients had a slightly better median progression free survival compared with elderly patients: median PFS 4.3 months (95% CI 3.9-4.3) compared to 3.5 months (95% CI 2.8 – 4.3) for elderly patients (Table 7).

Discussion

Although almost half of patients diagnosed with STS are aged >65 years, elderly patients only represented 12% of participants in EORTC clinical trials of first-line chemotherapy for advanced STS.(15) Furthermore, the median age of elderly in these studies was 68 years, which is relatively low. This is concordant with previous studies which have shown that elderly cancer patients account for less than one quarter of all participants in clinical trials.(18)

As expected, most elderly patients had a performance status of 0 or 1 due to strict eligibility criteria required for clinical trials. Good performance status (0 or 1) is an independent predictive factor for overall survival.(19) Lung and liver metastases were present with similar frequency in elderly and younger patients. Liver metastases are associated with poor response rates and worse overall survival in advanced STS treated with anthracyclines. (19)

Although tumours were most commonly histopathological grade 3, a significant proportion of tumours in elderly, and younger patients, were grade 2. Given that histopathological grade predicts development of metastases in adult STS, and all patients had advanced disease, a higher proportion of grade 3 tumours was anticipated.(8) It is conceivable that patients with rapidly progressive grade 3 tumours were excluded due to frailty. The high number of grade 2 tumours is also noteworthy given

that low histological grade is associated with lower response rates in advanced STS patients treated with anthracycline chemotherapy and improved overall survival(19, 20) Histological subtypes differed according to age group; synovial sarcomas were more common in young patients and MFH (UPS) was more frequent among elderly patients. Synovial sarcoma is associated with improved survival in advanced STS patients treated with anthracyclines, and longer PFS in those treated with ifosfamide-containing regimens. (19, 20) Conversely, MFH (UPS) is associated with reduced overall survival in patients treated with anthracyclines. (19)

A minority of patients in this analysis had received prior radiotherapy. This is unexpected given that pre-or post-operative radiotherapy is now recommended for the majority of patients with intermediate or high-grade tumours.(21) These results may reflect inaccurate data recording, lack of adherence with guidelines and changes in practice over the last few decades.(22)

Overall, elderly patients had shorter overall survival than younger patients. There was also a trend towards shorter progression free survival and lower response rates. Despite favourable baseline characteristics, these results demonstrate that older age (>65 years) is an adverse prognostic factor for patients with advanced STS treated with first-line chemotherapy. In reality, the heterogeneity of an unselected elderly STS population encountered in clinical practice is not directly comparable with these patients. A previous single-institution, retrospective review of 120 elderly advanced STS (excluding GIST) patients treated with first-line chemotherapy, most commonly single-agent doxorubicin (60%), described a slightly better RR of 20%, however, OS was 6.5 months (95% CI 4.7-8.3).(23) Another mono-institutional study of 134 elderly patients with advanced soft tissue sarcomas (primary scalp, trunk, girdles and extremities only) reported median OS of 7.3 months.(24) In this study, one quarter of patients had PS 2 (n=33, 25%). In addition, 40% of cases were high grade UPS (formerly MFH) or angiosarcomas and these tumours were associated with worse prognosis <6 months.(24) An additional retrospective study evaluated 197 advanced STS patients aged ≥75 years and reported a median PFS of 4 months (95% CI 2.9-5.1) and OS of 10.9 months (95% CI 8.3-13.5), however baseline characteristics were undistinguishable from patients receiving best supportive

care.(25) In this study, age ≥80 years, PS≥2 and number of metastatic sites were independent prognostic variables for OS.(25) The majority of patients received an anthracycline-based regime (63%) and patients were usually treated with single-agent chemotherapy (83%).(25)

Doxorubicin has been standard first-line chemotherapy for advanced STS since the 1970s, however, side-effects include myelosuppression, mucositis and cardiotoxicity. Empirical dose reductions are often used in patients who are 'frail' or have pre-existing comorbidities such as renal dysfunction, due to the risk of severe toxicity and hospitalisation. Previous studies have demonstrated a dose-response relationship with optimal anti-tumour activity at doses of ≥60mg/m^2 (administered every three weeks) and reduced efficacy at lower levels.(26, 27) Older patients may therefore be disadvantaged due to suboptimal treatment.

The combination of doxorubicin and ifosfamide has been shown to provide higher response rates, however no improvement in overall survival and at the cost of increased toxicity.(21) In EORTC STBSG clinical trials (62842, 62851, 62883, 62903 trials) 114 elderly patients were treated with combination therapy (Dox+Ifo). These patients had a median OS of 12 months (95% CI 9.59-14.88) and PFS 5 months (95% CI 3.09-6.41). There is often a misconception that elderly patients do not tolerate chemotherapy, however these results demonstrate that even doublet chemotherapy can be used effectively in carefully selected patients

We observed that radiological responses were mainly seen in elderly patients treated with doxorubicin or doxorubicin plus ifosfamide. It is probable that these patients were potentially the more 'fit' elderly patients who were considered to be suitable for clinical trials of these more toxic chemotherapy drugs. In addition, two-thirds of all elderly patients were treated with these chemotherapy regimens and therefore more responses may be anticipated in a larger group. The higher overall response rate in younger patients may be at least partly explained by greater proportion of patients aged <65 years

who received combination ifosfamide plus doxorubicin, which has a significantly higher response rate compared to single agent doxorubicin (16).

Determining which patients will tolerate chemotherapy is challenging. The ability of physicians to predict chemotherapy induced toxicity has been evaluated in lung cancer patients.(28) This group found that severe toxicity and successful completion of treatment were equally likely in patients who were deemed eligible for treatment.(28) They suggested that more detailed geriatric assessments are needed in order to predict those patients who are at risk of toxicity.(28) The effectiveness of such tools have been tested in other tumour groups. Mini-mental state examination (MMSE) and instrumental activities of daily living (IADL) were predictive of toxicity in elderly, metastatic colorectal cancer patients.(29) Comprehensive geriatric assessment (CGA) has been used in metastatic breast cancer patients (aged ≥65 years) to predict grade 3-4 toxicity.(30) The International Society of Geriatric Oncology (SIOG) consensus has determined the 'G8' assessment as the most 'robust, predictive/prognostic' tool for outcome measures in elderly patients.(31) The EORTC-STBSG are now routinely incorporating the G8 assessment tool in their clinical trials.

Participants in research studies must be representative the population of interest.(5) With an ageing population, there is increasing need for clinical trials which are designed to assess the optimal pharmacotherapeutic strategies for elderly patients. The feasibility of metronomic oral cyclophosphamide with prednisolone was evaluated in a group of 26 elderly patients (aged 66-88 years); toxicity profile was favourable, response rate was 26.9% and median PFS was 6.8 months.(32) Other trials include the 'EPAZ' phase II non-inferiority trial of pazopanib (800mg once daily) vs doxorubicin (75 mg/m^2) as first-line therapy for advanced STS patients aged ≥60 years (n=120) and the 'E-TRAB' study in elderly patients (aged >60 years), treated with first-line Trabectedin and considered unsuitable for anthracycline-based chemotherapy(n=110).(33, 34) The E-TRAB study will analyse quality of life and patient reported outcome data in addition to overall survival.(34)

The challenge is to design trials which are not only for 'elite' older patients but consider the heterogeneity of older patients. Although the median overall survival was inferior for elderly patients, response rates were similar, suggesting that elderly patients can derive benefit from standard chemotherapy regimens which are routinely prescribed for younger patients. Although the patients described in this report were of good performance status, our data can provide a benchmark for designing future trials. Study designs should also consider tools which can accurately assess potential toxicity of treatments and enable stratification of patients. These trials should be done within a multidisciplinary team, including geriatricians and trained nursing staff to provide adequate support for patients. Given the marginal survival benefit of chemotherapy in advanced STS, clinical trials should also incorporate health-related quality of life (HRQoL) assessments as study endpoints. This data will enhance clinical decision making and enable clinicians to provide a holistic, evidence-based approach to the care of elderly patients.

Although there were few patients in these EORTC-STBSG clinical trials aged ≥75 years, their outcomes were similar to those aged ≥65 years. It is probable that these patients were highly selected 'older-elderly' individuals in order to meet eligibility criteria for these clinical trials. In a 'real-life' setting the METASARC observational study (n=2,165) reported that patients aged ≥75 years (n=279) were significantly less likely to receive any systemic treatment for metastatic disease and more likely to be offered best supportive care than those aged <75 years.(35) This French group attributed this finding to the general 'reluctance' of oncologists to prescribe anthracyclines to elderly patients in view of potential haematological and cardio-toxic effects these drugs in older patients with functional decline or co-morbid medical conditions.(35) The complex association of cellular senescence, ageing and cancer is outwith the scope of this paper.

Limitations

The clincial trials in this EORTC-STBSG database were not designed to evaluate age-related differences in chemotherapy outcomes, therefore p-values are not presented in order to avoid over-interpretation the data. Selection bias due to the favourable baseline characteristics of clinical trial

patients means that these results may not reflect outcomes in clinical practice. No details were available on treatments received on progression of disease. However, due to the limited availability of effective 2nd/3rd line treatment options, it is likely that all patients will have received similar treatments. In addition, this database contains historical data from patients recruited in clinical trials from the 1980s and therefore results may be influenced by differences in concomitant standards of care.

Conclusion

Elderly patients with advanced STS have slightly worse outcomes than younger patients when treated with first line chemotherapy within clinical trials. In light of the ageing population, there is increasing need to design studies which specifically evaluate treatments in elderly patients, not only those with favourable characteristics. The results of this analysis can help in the design of future trials, incorporating geriatric tools to stratify patients and assess risk, and including health-related quality of life as endpoints.

Conflicts of Interest

The authors declare that there are no conflicts of interest regarding the publication of this paper.

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Table 1: Patient Characteristics	Age category		Total (N=2810) N (%)
	< 65 yrs (N=2462) N (%)	≥65 yrs (N=348) N (%)	
Performance status			
0	1122 (45.6)	134 (38.5)	1256 (44.7)
1	1127 (45.8)	177 (50.9)	1304 (46.4)
2+	187 (7.6)	32 (9.2)	219 (7.8)
Missing	26 (1.1)	5 (1.4)	31 (1.1)
Treatment*			
DOX 75	843 (34.2)	113 (32.5)	956 (34.0)
Caelyx	34 (1.4)	13 (3.7)	47 (1.7)
EPI 75	81 (3.3)	17 (4.9)	98 (3.5)
EPI 3*50	89 (3.6)	19 (5.5)	108 (3.8)
EPI 1*150	102 (4.1)	7 (2.0)	109 (3.9)
IFO 5	43 (1.7)	9 (2.6)	52 (1.9)
IFO 3*3	134 (5.4)	13 (3.7)	147 (5.2)
IFO 9 continu	98 (4.0)	4 (1.1)	102 (3.6)
DOX 50-IFO 5	533 (21.6)	78 (22.4)	611 (21.7)
DOX 75-IFO 5	234 (9.5)	36 (10.3)	270 (9.6)
DOX 75-IFO 10	220 (8.9)	0 (0.0)	220 (7.8)
Trabectedin	51 (2.1)	39 (11.2)	90 (3.2)
Histological Grading			
1	213 (8.7)	33 (9.5)	246 (8.8)
2	703 (28.6)	71 (20.4)	774 (27.5)
3	841 (34.2)	89 (25.6)	930 (33.1)
Missing	705 (28.6)	155 (44.5)	860 (30.6)
Histological Cell Type			
MFH/UPS**	239 (9.7)	55 (15.8)	294 (10.5)
Leiomyosarcoma	741 (30.1)	130 (37.4)	871 (31.0)
Liposarcoma	242 (9.8)	30 (8.6)	272 (9.7)
Synovial sarcoma	254 (10.3)	11 (3.2)	265 (9.4)

Fibrosarcoma	74 (3.0)	12 (3.4)	86 (3.1)
Rhabdomyosarcoma	56 (2.3)	3 (0.9)	59 (2.1)
Angiosarcoma	78 (3.2)	12 (3.4)	90 (3.2)
MPNST* **	127 (5.2)	7 (2.0)	134 (4.8)
Miscellaneous	398 (16.2)	45 (12.9)	443 (15.8)
Unclassified	160 (6.5)	21 (6.0)	181 (6.4)
Missing	93 (3.8)	22 (6.3)	115 (4.1)
Prior Surgery			
No	213 (8.7)	20 (5.7)	233 (8.3)
Partial	474 (19.3)	65 (18.7)	539 (19.2)
Total	482 (19.6)	69 (19.8)	551 (19.6)
Missing	1293 (52.5)	194 (55.7)	1487 (52.9)
Prior radiotherapy			
No	1677 (68.1)	201 (57.8)	1878 (66.8)
Yes	675 (27.4)	71 (20.4)	746 (26.5)
Missing	110 (4.5)	76 (21.8)	186 (6.6)
Site (s) of Disease involvement			
Primary site involved	1076 (43.7)	167 (48.0)	1243 (44.2)
Bone metastases	252 (10.2)	24 (6.9)	276 (9.8)
Liver metastases	420 (17.1)	63 (18.1)	483 (17.2)
Lung metastases	1417 (57.6)	181 (52.0)	1598 (56.9)
Other metastases	1003 (40.7)	139 (39.9)	1142 (40.6)

* **DOX 75** (doxorubicin 75mg/m^2), **Caelyx** (caelyx 35mg/m^2), **EPI 75** (epirubicin 75mg/m^2) **EPI 3*50** (epirubicin 50mg/m^2 [days 1-3]), **EPI 1*150** (epirubicin 150mg/m^2), **IFO 5** (ifosfamide 5 mg/m^2), **IFO 3*3** (ifosfamide 3mg/ m^2 [days 1-3]) **IFO 9 continu** (ifosfamide 9 mg/m^2 [continuous infusion over 72 hours])) **DOX 50-IFO 5** (doxorubicin 50mg/m^2 - ifosfamide 5 mg/m^2), **DOX 75-IFO 5** (doxorubicin 75 mg/m^2 - ifosfamide 5 mg/m^2) **DOX 75 – IFO 10** (doxorubicin 75 mg/m^2 - ifosfamide 10 mg/m^2), **TRAB** (1.3 mg/m², 3 hrs infusion or 1.5 mg/m², 24 hrs infusion).

**MFH/UPS –Malignant fibrous histiocytoma (now reclassified as undifferentiated pleomorphic sarcoma)

*** **MPNST** – Malignant peripheral nerve sheath tumour

Table 2: Best overall response elderly patients (all treatments)

Best Overall Response	Treatment Received					Total (N=348) N (%)
	Doxorubicin alone (N=126) N (%)	Doxorubicin+ ifosfamide (N=114) N (%)	Epirubicin (N=43) N (%)	Ifosfamide alone (N=26) N (%)	Trabectedin (N=39) N (%)	
Complete Response	1 (0.8)	3 (2.6)	0 (0.0)	0 (0.0)	0 (0.0)	4 (1.1)
Partial Response	21 (16.7)	18 (15.8)	2 (4.7)	2 (7.7)	5 (12.8)	48 (13.8)
Stable Disease	41 (32.5)	36 (31.6)	22 (51.2)	8 (30.8)	20 (51.3)	127 (36.5)
Progressive Disease	49 38.9)	33 (28.9)	15 (34.9)	10 (38.5)	13 (33.3)	115 (33.0)
Not evaluable	14 (11.1)	24 (21.1)	4 (9.3)	6 (23.1)	1 (2.6)	49 (14.1)
Survival status						
Alive	29 (23.0)	18 (15.8)	6 (14.0)	5 (19.2)	26 (66.7)	84 (24.1)
Dead	97 (77.0)	96 (84.2)	37 (86.0)	21 (80.8)	13 (33.3)	264 (75.9)
PFS status*						
Censored	5 (4.0)	9 (7.9)	3 (7.0)	0 (0.0)	0 (0.0)	17 (4.9)
Event	121 (96.0)	105 (92.1)	40 (93.0)	26 (100.0)	39 (100.0)	331 (95.1)

*Progression Free Survival Status.

Table 3: Overall survival elderly patients (all treatments)

Treatment	Patients (N)	Observ. Events* (O)	Median OS (95% CI) (Months)	% alive at 3 months (95% CI)	% alive at 6 months (95% CI)	% alive at 1 Year (95% CI)
Doxorubicin alone	126	97	9.76 (7.36,11.50)	83.1 (75.3,88.6)	62.9 (53.6,70.8)	40.1 (31.1, 49.0)
Doxorubicin + ifosfamide	114	96	12.06 (9.59,14.88)	87.6 (80.0,92.5)	79.5 (70.8,85.9)	51.8 (42.0, 60.7)
Epirubicin	43	37	9.86 (5.88,11.79)	74.4 (58.5,84.9)	64.8 (48.5,77.1)	35.3 (21.2, 49.7)
Ifosfamide alone	26	21	9.72 (2.86,14.39)	69.2 (47.8,83.3)	55.6 (34.0,72.7)	32.5 (14.8, 51.6)
Trabectedin	39	13	17.25 (9.40,17.25)	84.5 (68.6,92.7)	72.9 (55.4,84.5)	60.6 (37.0, 77.7)
All	348	264	10.78 (9.43,11.83)	82.6 (78.2,86.2)	69.2 (64.0,73.9)	44.0 (38.3, 49.5)

*Number of events observed

Table 4: Progression free survival elderly patients (all treatments)

Treatment	Patients (N)	Observ. Events* (O)	Median PFS (95% CI) (Months)	% at 3 months (95% CI)	% at 6 months (95% CI)	% at 1 Year (95% CI)
Doxorubicin alone	126	121	3.12 (2.07,4.14)	50.4 (41.4,58.8)	28.8 (21.2,36.9)	12.0 (7.1,18.4)
Doxorubicin + ifosfamide	114	105	5.22 (3.09,6.41)	61.3 (51.7,69.6)	44.2 (34.9,53.1)	21.8 (14.6,30.0)
Epirubicin	43	40	3.84 (1.41,6.21)	50.7 (34.9,64.5)	41.0 (26.2,55.2)	8.4 (2.3,19.8)
Ifosfamide alone	26	26	2.18 (1.38,3.81)	38.5 (20.4,56.3)	15.4 (4.8,31.5)	3.9 (0.3,16.4)
Trabectedin	39	39	2.79 (1.64,5.75)	48.7 (32.5,63.2)	30.8 (17.3,45.4)	5.1 (0.9,15.2)
All	348	331	3.48 (2.76,4.27)	52.9 (47.5,58.0)	34.5 (29.6,39.6)	13.4 (10.0,17.2)

*Number of observed events.

Table 5: Best overall response in elderly patients (≥65 years) versus younger patients (<65 years)

Treatment	Best overall response*					Total
	Not evaluable N (%)	CR N (%)	PR N (%)	NC N (%)	PD N (%)	N (100%)
Doxorubicin alone	**(N=78)**	**(N=19)**	**(N=153)**	**(N=392)**	**(N=361)**	**(N=1003)**
< 65 yrs	64 (7.3)	18 (2.1)	132 (15.1)	351 (40.0)	312 (35.6)	877
≥65 yrs	14 (11.1)	1 (0.8)	21 (16.7)	41 (32.5)	49 (38.9)	126
Doxorubicin + ifosfamide	**(N=111)**	**(N=51)**	**(N=245)**	**(N=426)**	**(N=268)**	**(N=1101)**
< 65 yrs	87 (8.8)	48 (4.9)	227 (23.0)	390 (39.5)	235 (23.8)	987
≥ 65 yrs	24 (21.1)	3 (2.6)	18 (15.8)	36 (31.6)	33 (28.9)	114
Epirubicin	**(N=22)**	**(N=10)**	**(N=35)**	**(N=122)**	**(N=126)**	**(N=315)**
< 65 yrs	18 (6.6)	10 (3.7)	33 (12.1)	100 (36.8)	111 (40.8)	272
≥65 yrs	4 (9.3)	0 (0.0)	2 (4.7)	22 (51.2)	15 (34.9)	43
Ifosfamide alone	**(N=39)**	**(N=0)**	**(N=31)**	**(N=117)**	**(N=114)**	**(N=301)**
< 65 yrs	33 (12.0)	0 (0.0)	29 (10.5)	109 (39.6)	104 (37.8)	275
≥ 65 yrs	6 (23.1)	0 (0.0)	2 (7.7)	8 (30.8)	10 (38.5)	26
Trabectedin	**(N=2)**	**(N=1)**	**(N=8)**	**(N=44)**	**(N=35)**	**(N=90)**
< 65 yrs	1 (2.0)	1 (2.0)	3 (5.9)	24 (47.1)	22 (43.1)	51
≥65 yrs	1 (2.6)	0 (0.0)	5 (12.8)	20 (51.3)	13 (33.3)	39

*CR- complete reponse, PR- partial response, NC – no change (stable), PD – progressive disease.

Table 6. Overall survival: Comparison elderly (≥65 years) versus younger (<65) patients

	Patients (N)	Observed Events (O)	Median (95% CI) (Months)	% at 6 months (95% CI)
All treatments				
< 65 yrs	2462	1997	12.32 (11.86, 12.85)	77.2 (75.5, 78.8)
>= 65 yrs	348	264	10.78 (9.43, 11.83)	69.2 (64.0, 73.9)
Doxorubicin alone				
< 65 yrs	877	700	11.79 (10.48, 12.71)	74.6 (71.6, 77.4)
>= 65 yrs	126	97	9.76 (7.36, 11.50)	62.9 (53.6, 70.8)
Doxorubicin + ifosfamide				
< 65 yrs	987	824	13.24 (12.42, 14.16)	82.1 (79.5, 84.4)
>= 65 yrs	114	96	12.06 (9.59, 14.88)	79.5 (70.8, 85.9)
Epirubicin				
< 65 yrs	272	229	11.17 (9.63, 12.16)	72.1 (66.3, 77.0)
>= 65 yrs	43	37	9.86 (5.88, 11.79)	64.8 (48.5, 77.1)
Ifosfamide alone				
< 65 yrs	275	231	11.14 (10.22, 12.62)	72.3 (66.5, 77.2)
>= 65 yrs	26	21	9.72 (2.86, 14.39)	55.6 (34.0, 72.7)
Trabectedin				
< 65 yrs	51	13	Not reached	81.6 (67.6, 90.0)
>= 65 yrs	39	13	17.25 (9.40, 17.25)	72.9 (55.4, 84.5)

Table 7. Progression free survival: Comparison elderly (≥65 years) versus younger (<65) patients

	Patients (N)	Observed Events (O)	Median (95% CI) (Months)	% at 6 months (95% CI)
All treatments				
< 65 yrs	2462	2318	4.27 (3.94, 4.57)	41.0 (39.0, 42.9)
>= 65 yrs	348	331	3.48 (2.76, 4.27)	34.5 (29.6, 39.6)
Doxorubicin alone				
< 65 yrs	877	827	3.65 (3.22, 4.17)	36.0 (32.8, 39.2)
>= 65 yrs	126	121	3.12 (2.07, 4.14)	28.8 (21.2, 36.9)
Doxorubicin + ifosfamide				
< 65 yrs	987	921	6.18 (5.62, 6.60)	51.2 (48.0, 54.3)
>= 65 yrs	114	105	5.22 (3.09, 6.41)	44.2 (34.9, 53.1)
Epirubicin				
< 65 yrs	272	253	2.89 (2.33, 3.42)	33.5 (27.9, 39.1)
>= 65 yrs	43	40	3.84 (1.41, 6.21)	41.0 (26.2, 55.2)
Ifosfamide alone				
< 65 yrs	275	266	2.76 (2.43, 3.09)	28.0 (22.8, 33.4)
>= 65 yrs	26	26	2.18 (1.38, 3.81)	15.4 (4.8, 31.5)
Trabectedin				
< 65 yrs	51	51	2.99 (1.54, 6.14)	37.3 (24.3, 50.2)
>= 65 yrs	39	39	2.79 (1.64, 5.75)	30.8 (17.3, 45.4)

Summary of EORTC-STBSG Clinical Trials: Elderly Patients per Protocol (Appendix)

EORTC Study	Elderly patients(n)	References
62801	41	Mouridsen HT, Bastholt L, Somers Rt et al. Adriamycin versus epirubicin in advanced soft tissue sarcomas. A randomized phase II/phase III study of the EORTC Soft Tissue and Bone Sarcoma Group. Eur J Cancer Clin Oncol. 1987 Oct;23(10):1477-83
62842	16	Schütte J, Mouridsen HT, Stewart W et al. Ifosfamide plus doxorubicin in previously untreated patients with advanced soft tissue sarcoma. The EORTC Soft Tissue and Bone Sarcoma Group. Eur J Cancer. 1990;26(5):558-61.
62851	66	Santoro A, Tursz T, Mouridsen H et al. Doxorubicin versus CYVADIC versus doxorubicin plus ifosfamide in first-line treatment of advanced soft tissue sarcomas: a randomized study of the European Organization for Research and Treatment of Cancer Soft Tissue and Bone Sarcoma Group. J Clin Oncol. 1995 Jul;13(7):1537-45.
62883	14	Steward WP, Verweij J, Somers R et al. Doxorubicin plus ifosfamide with rhGM-CSF in the treatment of advanced adult soft-tissue sarcomas: preliminary results of a phase II study from the EORTC Soft-Tissue and Bone Sarcoma Group. J Cancer Res Clin Oncol. 1991;117 Suppl 4:S193-7.
62901	40	Nielsen OS, Dombernowsky P, Mouridsen H et al. High-dose epirubicin is not an alternative to standard-dose doxorubicin in the treatment of advanced soft tissue sarcomas. A study of the EORTC soft tissue and bone sarcoma group. Br J Cancer. 1998 Dec;78(12):1634-9.
62903	45	Le Cesne A, Judson I, Crowther D et al. Randomized phase III study comparing conventional-dose doxorubicin plus ifosfamide versus high-dose doxorubicin plus ifosfamide plus recombinant human granulocyte-macrophage colony-stimulating factor in advanced soft tissue sarcomas: A trial of the European Organization for Research and Treatment of Cancer/Soft Tissue and Bone Sarcoma Group. J Clin Oncol. 2000 Jul;18(14):2676-84.
62912	19	van Oosterom AT, Mouridsen HT, Nielsen OS et al. Results of randomised studies of the EORTC Soft Tissue and Bone Sarcoma Group (STBSG) with two different ifosfamide regimens in first- and second-line chemotherapy in advanced soft tissue sarcoma patients. Eur J Cancer. 2002 Dec;38(18):2397-406
62941	4	Verweij J, Lee SM, Ruka W et al. Randomized phase II study of docetaxel versus doxorubicin in first- and second-line chemotherapy for locally advanced or metastatic soft tissue sarcomas in adults: a study of the european organization for research and treatment of cancer soft tissue and bone sarcoma group. J Clin Oncol. 2000 May;18(10):2081-6.
62962	22	Judson I, Radford JA, Harris M et al. Randomised phase II trial of pegylated liposomal doxorubicin (DOXIL/CAELYX) versus doxorubicin in the treatment of advanced or metastatic soft tissue sarcoma: a study by the EORTC Soft Tissue and Bone Sarcoma Group. Eur J Cancer. 2001 May;37(7):870-7.
62971	7	Lorigan P, Verweij J, Papai Z, et al. Phase III trial of two investigational schedules of ifosfamide compared with standard-dose doxorubicin in advanced or metastatic soft tissue sarcoma: a European Organisation for Research and Treatment of Cancer Soft Tissue and Bone Sarcoma Group Study. J Clin Oncol. 2007 Jul 20;25(21):3144-50
62061	20	Gelderblom H, Blay JY, Seddon BM et al. Brostallicin versus doxorubicin as first-line chemotherapy in patients with advanced or metastatic soft tissue sarcoma: an European Organisation for Research and Treatment of Cancer Soft Tissue and Bone Sarcoma Group randomised phase II and pharmacogenetic study. Eur J Cancer. 2014 Jan;50(2):388-96.
62091	54	Bui-Nguyen B, Butrynski JE, Penel N et al. A phase IIb multicentre study comparing the efficacy of trabectedin to doxorubicin in patients with advanced or metastatic untreated soft tissue sarcoma: the TRUSTS trial. Eur J Cancer. 2015 Jul;51(10):1312-20.
62012	0	Judson I, Verweij J, Gelderblom H et al. Doxorubicin alone versus intensified doxorubicin plus ifosfamide for first-line treatment of advanced or metastatic soft-tissue sarcoma: a randomised controlled phase 3 trial. Lancet Oncol. 2014 Apr;15(4):415-23.