



Metastatic Soft Tissue Sarcomas in Elderly Patients: 18 Years of Monoinstitutional Experience

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Abstract

Elderly people represent more than 50% of sarcoma patients, but very few data are available on the results of treatment of this population. Aged population is a complex group of patients because of different general conditions, presence of comorbidities, polypharmacy, and mental and social status. A Comprehensive Geriatric Assessment (CGA) can help in decision making. In our series people had metastatic or locally advanced non operable disease. One hundred thirty four patients receive done line of chemotherapy. Sixty two a second line. Monotherapy was the most common treatment. Dose reduction was necessary in most of patients. Only one complete remission was seen in first line therapy. Median survival was 7.3 months. Toxicities after dose reduction was mild in conclusion elderly patients with metastatic STS have a poor prognosis. Our study emphasize the need of multidisciplinary approach and to plan specific studies to define the best approach in this specific group of patients.

Introduction

Adult soft tissue sarcomas are rare solid tumors arising from connective tissues. More than 50 different cytotypes are reported. They account for 1% of all cancer, with an incidence of 3-4 cases per 100000 [1]. About 50% of those tumors are diagnosed in patients over 65 years and age at presentation determines survival [2] even if the behaviour of STS in elderly patients is poorly investigated and described. The rarity of STS, the heterogeneity of this tumor, and the difficult approach that request a multidisciplinary team, poses a challenge to the physician, being difficult to predict the prognosis and the response to therapy for the different subtypes [3]. Many Clinicians, even in referral centers believe that old patients are poorly tolerant of anesthesia, surgery, chemo and radiotherapy [4,5]. In clinical studies elderly patients are under represented or not included, and many of the literature evidences are retrospective [4]. General conditions of the patients, concurrent morbidities, poor familial and social support (caregiving), polypharmacy are additional problems that are recorded in elderly population with STS [4,6,7]. As population ages, old patients cancer care has become a great challenge worldwide. Since adult STS has a bimodal presentation in young people (25-54 years) and in elderly population (over 65 years) different problems of care face the multidisciplinary team. Moreover, in the old population we distinguish three different categories: fit, vulnerable and frail [6].

We conducted this retrospective, monoinstitutional study hold in an Italian referral center for diagnosis and care of STS to describe the activity and feasibility of first and second line chemotherapy in elderly patients with metastatic soft tissue sarcomas.

Patients and Methods

Patients with metastatic STS aged >65 years diagnosed from February 1998 to December 2015 were considered in this retrospective monoinstitutional study. All patients had a histologically confirmed, non operable or metastatic STS of the extremities. Primary STS of the scalp, trunk, girdles and extremities were considered. Retroperitoneal, uterine, visceral, lung and mediastinal STS were excluded from this analysis. Mixoid and round cell liposarcoma were the most represented histological types (46 cases), leiomyosarcoma were the second most common subtypes, pleomorphic undifferentiated sarcomas was the third in frequency, Angiosarcoma, Mixofibrosarcoma [8], MPNST [5], synovial sarcoma [3] other histologies [8]. Patient with Ewing Family sarcomas, Rhabdomyosarcoma and GIST were excluded. Retroperitoneal sarcomas, mediastinal or lung sarcomas and gynecological sarcomas were not included. Patients were followed in the institutional prospective data base: age of the patient, date of diagnosis of primary tumor, histology, data of

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relapse or metastasis, site of metastasis, administered chemotherapy as first and second line, comorbidities, comprehensive Geriatric score if available (CGA), date of death or of the last follow up were reported [7]. When chemotherapy was initiated lung were the most common site of the secondary event in 117 patients (88%), soft tissues in 22 patients (29%), nodes in 17 cases (22%), bone in 12 cases (17%). SNC metastasis in 5 patients (3%) were rare and in general represented the terminal event. 26 patients had more than 1 metastatic site. The clinical outcome were adjourned at December 31, 2015. Overall survival was the principal end point calculated from the start of chemotherapy to the last date of follow up or death. Response rate, toxicities related to type of administered chemotherapy were the secondary end points.

Results

One hundred ninety six patients with 65 years or older were considered. Forty six of them did not receive chemotherapy because of bad general conditions, frailty, more than 3 comorbidities, insufficient renal, bone marrow or liver functions. Compromised cognitive functions determined the exclusion of 16 patients.

As a consequence 134 patients older than 65 years were considered in our study. 85 were young elderly (65-70 years) 34 were in the range between 71 and 75, the other 15 >76 years. Seventy nine were males and 55 females.

All patients had a metastatic or inoperable relapsed disease. Performance status was ECOG 0-1 in 101 patients, ECOG 2-3. GCA was done in 46 patients (34%), 13 patients were declared vulnerable following the current classification [6,7]. All the other were in good conditions and were treated as younger patients. 27% of patients had reduced renal activity with eGFR <90 ml/min. Eighty-nine (67%) of patients had a surgical intervention of the primary STS. 22 (30%) received a second surgery after local relapse. Only 10 patients (14%) were resected for metastatic lung disease. All of those relapsed and received chemotherapy. All the patients received at least one course of chemotherapy, median number 3 (range 1-12).

Adriamycin or Epirubicin was used in 73% of patients: 25% of them received full of the planned dose therapy, the other were treated with a reduced dose (ranging from 10-25% of the theoretic dose) [8,9]. Ifosfamide as continuous 14 days infusion q 28 days, was administered in 18 as first line (29% of cases) [10]. The combination between Antracycline and Ifosfamide + Mesna because of its high degree of toxicity was administered in 4 patients only for no more than 3 cycles (range 1-3). GCSF support and reduction of doses were always necessary [4,11]. In angiosarcoma (14 patients) the first line chemotherapy was weekly paclitaxel [4,12]. Second line chemotherapy was administered in 62 patients only, most of them in the age 65-70 (83%). 16% were 71-75 and only 2 >76.

Ifosfamide + Mesna in 14 days C.I. was utilized in 34 (54%) patients who progressed after first line chemotherapy [10]. Trabectedin has been approved since 2010 as second line therapy and 11 (17%) patients received treatment as second or further line of therapy as 24 hour infusion in Liposarcomas and leiomyosarcoma [13,14]. Gemcitabine alone d 1,8 every 21 was given as second or third line in 13 (21%) patients with metastatic leiomyosarcoma [15].

Pazopanib was prescribed in 4 patients as third line. Three patients received reduced doses (400 mg instead 800) because of the toxicity [16,17]. Seventy five percent of second line chemotherapy was administered at reduced doses to avoid side effects. No toxic death were recorded. 15 (12%) patients were recovered for febrile

neutropenia, thrombocytopenia and mucositis. At the time of this analysis only 14 patients were alive (10%). In the first line therapy we recorded 1 CR, 14 PR and 43 SD. Median OS was 7.3 months. In second line therapy no CR were seen, 4 over 62 patients showed a PR and 23 a stable disease. Bad PS, low score in CGA, vulnerability, number of metastasis were negative prognostic factors. Dose reduction and toxicity were prognostic factors. Median Survival time for younger population with metastatic soft tissue sarcomas ranges from 10 to 13 months. Leiomyosarcoma and mixoidliposarcomas had a better prognosis with a median overall survival >10 months. On the contrary UPS, MPNST had worse results with no CR and OS less than 6 months. As first line chemotherapy over 134 patients the total dose intensity for Antracyclines was 65%, for Ifosfamide c.i. was 67% and weekly Paclitaxel in angiosarcomas had a D.I. of 69%. In second line chemotherapy only Trabectedin (71%) and Gemcitabine (64%) had a D.I. >50%.

Discussion

In inoperable, advanced or metastatic soft tissue sarcoma the therapeutic goal is to achieve a control over the disease, without heavy side effects. Chemotherapy is the main treatment in stage IV disease, although in some case of limited pulmonary metastasis surgery can be purposed [4,17-19]. More than 50% of STS are diagnosed in patient over 65 years but in daily clinical practice few data are available in this setting [4,18-20]. There is a widespread opinion that older patient with STS is undertreated in confront with the young patients and this can worsen the prognosis [4,18-20]. Less radical interventions, less adjuvant radio or chemotherapy, less adequate postoperative surveillance and at last less intensive and active chemotherapy in case of metastatic relapse are the reasons of those unsatisfactory results [4,19,20]. Elderly patients with stage IV STS have a worse prognosis for multiple reasons related to the presentation of the disease, patients conditions and social and familial problems [7,21]. In old patients STS are in general larger and higher grade tumors than in younger. Age can be associated with a less active cell mediated immunity [18,20]. In our series Mixoid liposarcomas and leiomyosarcomas represented 48% of the cases, but 40% were high grade UPS and angiosarcomas.

In Yousaf and coll (and in the Van der Graaf and coll series the more aggressive histotypes were the great majority of cases [18,19]. In our series median survival was 7.3 months Yousaf and Coll reported a similar survival of 6,5 months [18], Van der Graaf and coll in the EORTC study [19] had a better survival of 9,8 months, but median age was lower with less comorbidity. Leiomyosarcomas had a better survival both in our (>10 months) or in Yousaf patients [18]. The principles of treatment for elderly patients are similar to those described for younger patients [3].

Surgery is the preferential choice in localized disease, but frequently is suboptimal because the surgeon can be reluctant to perform and the patient to accept a wide or radical surgery [20,22]. Moreover in locally advanced, relapse or metastatic disease, surgical approach is seldom offered to the elderly patient [20]. In our series only 30% of the patients received surgery on lung metastasis. General conditions and comorbidities play an important role in therapy decision making [4,6,7]. Many patients are in mild performance status, in our group of patients 25% were PS 2. In most patients with metastatic STS two or more morbidities are concomitant, and administration of chemotherapy decreases with age (4,23). Only 11% of our patients older than 75 years received a chemotherapy regimen. In Yousaf study patients with comorbidities, poor nutritional

conditions, hypoalbuminemia and anemia predict a worse response to therapy and prognosis [18]. Polychemotherapy is more toxic than single agent therapy and Anthracyclines and Alkylating agents have worse side effects than Gemcitabine or Trabectedine [4,8,9,13-15]. Moreover the two former drugs can be administered at a higher dose, for a more prolonged time of treatment [13-15]. Metronomic therapy with Cyclophosphamide can be safely administered but with low results [23], while TKI agent Pazopanib in elderly patients is poorly tolerated with asthenia, diarrhea and skin rash [17]. Social and familial problems play a pivotal role in administration and acceptance of medical therapy in elderly patients [4,7,24,25]. As well defined in CGA (comprehensive geriatric assessment) the global situation of elderly patient must be considered evaluating health, psychosocial and functional capabilities. CGA is a multidimensional and multispecialistic tool that can detect problems omitted in normal clinical assessment. Unfortunately the current CGA is a complex tool with nine different items to be detected, difficult to adopt in the busy everyday practice. As a consequence only few patients have been evaluated with the CGA questionnaire in our (34%) as well as in other studies [7,24,25]. The present study has some limitations: it is a monoinstitutional and a retrospective study, even in a referral Center.

Patients have been enrolled in 16 years time and the multimodality treatment as well as the pharmacological agents changed during this period. For instance Trabectedin was approved in STS therapy only in 2009, Pazopanib in 2013.

Both drugs can have space in elderly patients treatment [13,14,16,17]. Second line chemotherapy in STS wasn't considered until 2013, now is routinely prescribed [9,11,13-18,20]. Early and continuous supportive care is a recent acquisition in Medical Oncology that allows prolonged treatment of chemotherapeutic agents with less toxicity [26]

All those improvement in care have sensibly changed the scenery even in a difficult setting as metastatic STS in elderly patients. Despite these progresses metastatic STS in elderly patients have a poor prognosis and under treatment of fit elderly patients remains common in daily practice [4,18-20]. Few controlled studies are available and small number of elderly patients are introduced in clinical trials for STS [3,4]. The appropriate selection of the patient and accurate evaluation of CGA are rare in Literature [7,12]. High stage and high grade sarcomas, less dose intensity and less aggressive treatment, lead to a worse prognosis and shorter survival and emphasize the need for specific controlled studies in elderly patients [22,23].

The reference Centers should guarantee a multidisciplinary approach involving Oncologists, Orthopaedics, Surgeons, Pathologist, Radiotherapists and Geriatricians and the decision has to be shared with the patient and his family [3,4,22]. Only this integrated care model and allowing the patient to express his priorities can clarify treatment goals and readjust the target of the treatment plan.

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