Retrospective Study Of Survival Benefit Of Second Line Chemotherapy In Adult Soft Tissue Sarcomas

Thesis

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Retrospective Study Of Survival Benefit Of Second Line Chemotherapy In Adult Soft Tissue Sarcomas

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Soft tissue sarcomas (STS) are relatively rare heterogeneous group of mesenchymal neoplasms that may arise in soft tissue, skin or various organs, and show a broad range of differentiation, such as smooth muscle (leiomyosarcoma), adipocyte (liposarcoma), striated muscle (rhabdomyosarcoma), endothelium (angiosarcoma) or fibroblast (e.g., dermatofibrosarcoma). The aim of the work is to evaluate soft tissue sarcoma patients at Ain Shams University Clinical Oncology Department and Agoza Police Hospital in the last five years (2011-2015) as regards incidence, site, pathological types, response to second line chemotherapy and toxicity, progression free survival and overall survival. This is a retrospective study of patients with STS of different cell types and various sites of origin represented at Ain Shams University Clinical Oncology Department and Agoza Police Hospital in the last five years (2011-2015)**Inclusion criteria** Age ≥ 18 years.; Pathologically proven STS.; Radiological or clinical proven metastasis; Patient progressed on first line metastatic chemotherapy. **Exclusion criteria:** Patients with, Dermatofibrosarcoma protuberans; Kaposi's sarcoma; Gastrointestinal stromal tumors; Desmoids tumors (aggressive fibromatosis); Co-morbidities interfering or contraindicated with appropriate chemotherapy regimens. This is retrospective study included 34 patients with soft tissue sarcoma (STS). The mean age of the patients was 40.9±13.4 years, ranging from 19 to 64 years with male predominance67%. There was an obvious histological diversity where synovial sarcoma was the most frequent type (29.4%) followed by liposarcoma and spindle cell sarcoma. Higher tumor grade was more common (59%) and distant metastases was detected in 18 patients (53%); more commonly with grade 3disease. Surgical treatment was adopted in 29 patients including only 2 amputations. Surgical margin was positive in 18/29 patients (62.1%). Palliative radiotherapy was used in 15 patients (44.1%). The most commonly used 1st line chemotherapy protocol was Ifosfamide + Adriamycin. Response after surgery and 1st line CTH was complete or partial remission in only 50% cases. Remission rate was apparently higher in patients with negative margin.

Key words : STS: soft tissue sarcoma; AJCC: American committe on cancer

Introduction

Soft tissue sarcomas are malignant tumors that arise in any of the mesodermal tissues and represent 1% of adult malignancies and 12% of pediatric malignancies. The most common sites are the extremities (50%), trunk and retroperitoneum (40%), or head and neck (10%), the anatomic sites of primary disease represent an important variable that influence treatment and outcome. The reported international incidence rates range from 1.8 to 5 per 100,000 per year ***(Wibmer et al., 2010)***

Incidence of most types of STS increases progressively with age. The median age at diagnosis is 50 years with estimated new cases and deaths from soft tissue sarcoma in the United States in 2015, 11,930 and 4,870 respectively ***(Atlanta et al., 2015)***.

The most soft tissue sarcomas are believed to be sporadic and have no clearly cause but in small proportion of cases, researchers have identified various associated risk factors including genetic factors, prior radiation therapy, lymphedema and several chemical agents ***(Helman LJ et al., 2014).***

Soft-tissue sarcomas (STSs) consist of approximately 50 different histological subtypes and have differing clinical behavior and response to chemotherapy. The most common types of STS are undifferentiated pleomorphic sarcoma, leiomyosarcoma, synovial sarcoma and peripheral nerve sheath tumor ***(Sharon W et al., 2012).***

The pathological features that define grade include cellularity, differentiation, pleomorphism, mitotic index and necrosis. The two most important factors are mitotic index and extent of necrosis ***(Goldblum et al., 2013).***

There are also ongoing developments in establishing biomarkers to allow further personalization of therapy (EWSR1-ATF1 in clear cell sarcoma and TLS-CHOP in myxoid or round cell sarcoma)as many types of sarcoma are associated with characteristic genetic aberrations including single base-pair substitutions, deletions, amplifications, and translocations ***(Antonescu et al., 2006)***.

An essential element of the work up of sarcoma is a history and physical examination, imaging of the primary tumor and distant metastasis by MRI in extremities sarcoma, CT in retroperitoneal sarcoma**.** STS most commonly metastasizes to

the lung, Tumors arising in the abdominal cavity more commonly metastasizes to liver and peritoneum ***(Casali, P. G., and J-Y.Blay et al., 2010).***

Pretreatment core needle or open incisional biopsy is highly preferred for diagnosis and grading of STS but FNA can be difficult to make an accurate primary diagnosis ***(Domanski et al., 2007)***.

AJCC staging system for STS has historically used a four grade system but within the staging groups this effectively functioned as 2 titred system (low and high grade). The two most widely used grading systems are NCI system and FNCLCC system, both are three-tier systems(low, intermediate high grade), in fact neither FNCLLC nor NCI system has been formally endorsed by either WHO or the association directors of anatomic and surgical pathology ***(Coindre et al., 2006).***

In the advanced disease setting (locally advanced, inoperable or metastatic) palliative chemotherapy is the mainstay of treatment, whereas the goal of surgery and radiotherapy is local control of the tumor, the aim of

chemotherapy is systemic control, which may be therapeutic, adjuvant, or palliative ***(Mytelka et al., 2016)***.

Doxorubicin and ifosfamide are, by consensus, the standard first line therapy in advanced soft tissue sarcoma. Docetaxel and gemcitabine appear to be associated with some activity and tolerability in the doxorubicin/ifosfamide refractory patients ***(Clin Oncol et al., 2007).***

Combination chemotherapy in our practice is largely reserved for those with rapidly progressing metastatic disease or inoperable soft tissue sarcoma where response may render disease resectable. In a recent meta-analysis, three-randomized phase III trials were identified comparing combination chemotherapy regimens containing ifosfamide with regimens without ifosfamide. This analysis revealed that the addition of ifosfamide to a chemotherapy regimen significantly improved response rates but did not produce a significant difference in 1 year survival. Higher rates of adverse events, including myelosuppression and death, were observed in patients who received combination chemotherapy ***(Ludwig, et al., 2008)***.

Taxanes, such as paclitaxel have been reported to have activity in vascular sarcoma and also docetaxel in combination with gemcitabine has been shown to be effective cytotoxic agents against sarcomas and associated with improvement of PFS and OS as second line in advanced STS ***(Maki et al., 2007)***.

There is ongoing work on the potential use of molecular targeted therapies such as pazobanib that has recently emerged as an effective TKI agent in patients who have progressed on an anthracycline and ifosfamide antiangiogenic agents, IGF1-R, HDAC, and mTOR inhibitors ***(Aranha and Agulnik et al., 2008)***.

AIM OF THE WORK

The aim of the work is to evaluate soft tissue sarcoma patients at Ain Shams University Clinical Oncology Department and Agoza Police Hospital in the last five years (2011-2015) as regards incidence, site, pathological types, response to second line chemotherapy and toxicity, progression free survival and overall survival.

EPIDEMIOLOGY AND ETIOLOGY

Soft-tissue sarcomas (STS) are rare malignant mesenchymal tumors with an extremely diverse range of clinical behaviors and represent 1% of adult malignancies and 12% of pediatric malignancies ***(Siegle et al., 2015).***

Estimated new cases and deaths from soft tissue sarcoma in the United States in 2016 are 12,310 and 4,990, respectively ***(Siegle et al., 2016).*** In Europe, the estimated incidence of soft tissue sarcoma was approximately 4-5/100000 people per year ***(Stiller et al., 2013).***

In Egypt, based on the results of National Cancer Registry Program, incidence rate of soft tissue sarcoma was reported to be 1.7 per 100,000 person-years among males and 1.7 among females ***(Ibrahim et al., 2014).***

Soft tissue sarcomas may occur at any age, and although most common in middle aged and older adults, they are relatively more common in children and young adults accounting for 7-10% of pediatric malignancies. They are an

important cause of death in the 14-29 years age group ***(Geraci et al., 2007).***

Most soft-tissue sarcomas are sporadic; few have an identifiable cause. There is an association between certain viral infections (notably Epstein – Barr virus in those with AIDS) and leiomyosarcoma ***(Singer et al., 2011)***

Prior radiation therapy (RT) to the affected area is a risk factor for the development of STS ***(Penel et al., 2008).*** Other factors associated with Soft tissue sarcoma development include long-standing lymph edema, exposure to arsenical pesticides and medications, herbicides, immunosuppressive drugs, alkylating agents, androgen-anabolic steroids, human immunodeficiency virus, and exposure to human herpes virus type 8 ***(Gessan et al., 2005).***

Children with hereditary retinoblastoma (owing to a germ-line mutation in the RB1tumor-suppressor gene) face an exceptionally high risk of osteosarcoma and soft-tissue sarcoma, which is further increased by the receipt of radiotherapy ***(Kleinerman et al., 2007).***