Retrospective Study of Second Line Chemotherapy in adult Soft Tissue Sarcomas Single centre experience (NEMROCK)

Thesis

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BY

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Abstract

Background: Soft-tissue sarcomas (STS) are rare malignant mesenchymal tumors. For most patients, the aetiology is unknown. Diagnostic methods include Biopsy, Imaging Methods, Immunohisto-chemistry and Cytogenetics. The goal of treatment for soft tissue sarcomas is to optimize oncologic outcome and maximize functional restoration by surgery, radiotherapy and chemotherapy.

Objective: Is to evaluate soft tissue sarcoma patients at NEMROCK in the last five years as regards incidence, pathological types, response to chemotherapy, disease free survival and overall survival.

Methods: All patients diagnosed with soft tissue tumors presented during the period between {January 2005 to December 2009} were included retrospectively (total 106 patients). Clinico-epidemiological analysis including age, sex, gender, site, pathology, chemotherapy both first and second line, response to treatment, progression free survival and overall survival.

Results: Males representing (57.5%) and Females representing (42.5%) of all patients, males: females ratio was 1.35: 1. Regards pathology, liposarcoma 19.81% and synovial sarcoma 16% and malignant fibrous histiocytoma 15% of all patients. Anthracycline based combination chemotherapy is mainly used in our center. 37 patients (34.9%) received first line chemotherapy most of patients respond by partial response to first line chemotherapy. Percentage of patients received second line chemotherapy to total soft tissue tumors patients was 11.32%. Disease progression is the most frequent response. Patients received cisplatin-vepside and carboplatin-vepside representing 83.33 % of the patients received second line and the response is almost progression.

Conclusions: the use of second line chemotherapy still needs more studies before judgment on its efficacy in soft tissue sarcoma treatment. cisplatin and vepside use in adult soft tissue sarcomas is ineffective as a second line chemotherapy.

Keywords: Soft tissue sarcoma, Second line chemotherapy

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List of abbreviations

ASPS	Alveolar soft-part sarcoma
BPNSTs	benign peripheral nerve sheath tumors
CD	cluster of differentiation
CNB	Core needle biopsy
CT	Computerized Tomography
CR	complete response
DBA	Diamond-Blackfan anemia
DFS	disease free survival
DFSP	Dermatofibrosarcoma protuberans
ES	Epithelioid Sarcoma
EORTC	European organization for research and treatment of cancer
EBRT	external beam radiotherapy
FDA	Food and Drug Administration
FNA	Fine needle aspiration
FNAB	Fine needle aspiration biopsy
FDG	fluorodeoxy glucose
GD	Gemcitabine and docetaxel
GM-CSF	granulocyte-macrophage colony-stimulating factor
GTP	gemcitabine triphosphate
GISTs	gastrointestinal stromal tumors
Gy	Gray
GOG	Gynecologic Oncology Group
HDI	high-dose ifosfamide
IMRT	intensity modulated radiotherapy
IV	intravenous
KS	Kaposi sarcoma
LMS	leiomyosarcoma
MPNST	malignant peripheral nerve sheath tumor
MFH	Malignant fibrous histiocytoma
MRI	Magnetic resonance imaging
NCI	National cancer institute
NOS	not otherwise specified
OS	overall survival
PR	partial response
PFS	progression free survival
PDGFR	platelet-derived growth factor receptor
PD	progressive disease

PET	Positron Emission Tomography
PNET	primitive neuroectodermal tumor
RR	response rate
RECIST	Response Evaluation Criteria in Solid Tumors
RT	radiotherapy
SARC	Sarcoma Alliance for Research through Collaboration
SMA	smooth muscle actin
STS	soft tissue sarcoma
SD	stable disease
TKIs	tyrosine kinase inhibitors
US	united states
Ups	undifferentiated pleomorphic sarcoma
HIV	human immunodeficiency virus
VEGFR	vascular endothelial growth factor receptor
WHO	World Health Organization

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Introduction

Soft tissue sarcomas (STS) are rare malignant mesenchymal tumors with an extremely diverse range of clinical behaviors, they are said to compress no more than 1% of all cancers, with an overall incidence of 30-40 per million per year ***(Jemal et al., 2004)***

Locally advanced or metastatic soft tissue sarcoma represents an incurable disease in the majority of patients not amenable to surgery with curative intent ***(Gadd et al, 1993; van Geel et al, 1996; Gutman et al, 1997)***.

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 ***(Clark et al., 2005)***.

Unfortunately, approximately 40% of patients with soft tissue sarcoma will develop local or distant disease recurrences ***(Weitz et al., 2003),*** and systemic chemotherapy with palliative intent is conventionally used to treat the metastatic disease ***(Cormier et al., 2004)***.

Several chemotherapeutic agents have been used for treating soft tissue sarcomas as a first line and as a second line, Doxorubicin and ifosfamide, either alone or in combination, have served as the backbone for metastatic sarcoma therapy for over 15 years. Two useful pairings of other chemotherapeutic agents and sarcoma subtypes found over the last 15 years of testing include taxanes ***(Fury et al., 2005)*** and the novel chemotherapeutic agent trabectedin ***(Le Cesne et al., 2005; Fayette et al., 2006; Grosso et al., 2006; Huygh et al., 2006)***. The chemotherapeutic combination of gemcitabine and docetaxel has been shown to be an effective combination of cytotoxic agents against sarcomas ***(Maki et al., 2007)***.

Aim of the work

The aim of the work is to evaluate soft tissue sarcoma patients at NEMROCK in the last five years as regards incidence, pathological types, response to chemotherapy, disease free survival and overall survival.

Epidemiology

Soft-tissue sarcomas (STS) are rare malignant mesenchymal tumors with an extremely diverse range of clinical behaviors. They are said to comprise no more than 1% of all cancers, with an overall incidence of 30–40 per million per year ***(Jemal et al., 2004)***. Men are more frequently affected than women ***(Jemal et al., 2005)***.

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 paediatric malignancies. They are an important cause of death in the 14-29 years age group ***(Albritton and Bleyer, 2003; Birch et al., 2003; Geraci et al., 2007; Ferrari and Bleyer, 2007).***

For the vast majority of cases, the aetiology is unknown, although there are certain genetic associations, such as the 10% lifetime risk of malignant peripheral nerve sheath tumor (MPNST) in individuals with familial neurofibromatosis, caused by mutations in the NF1 gene ***(Rasmussen and Friedman, 2000).***

Risk factors of soft tissue sarcoma are only partly known and include a family history of soft tissue sarcoma, certain genetic syndromes, exposure to ionizing irradiation, and exposure to certain chemicals such as vinyl chloride,Other factors associated with Soft tissue sarcoma development include long-standing lymphedema, 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 ***(Zahm and Fraumeni, 1997; Olsson, 1999).***

Malignant fibrous histiocytoma, angiosarcoma, and other mesenchymal subtypes have also been reported after therapeutic radiation ***(Robinson et al., 1988; Brady et al., 1992; Pitcher et al., 1994)***.

Diamond-Blackfan anemia (DBA) is a congenital pure red cell aplasia and in a registry study encompassing 354 individuals having the syndrome, 6 individuals had developed malignancies (3 osteosarcomas, 1 myelodysplastic syndrome, 1 colon cancer and 1 STS). The authors suggest that sarcoma risk is elevated in the gene carriers ***(Lipton et al., 2001).***

As synovial sarcomas are characterized by a translocation between (X; 18) it was hypothesized in a study that the translocation of the X-chromosome only affects the active X-chromosome, and as women have one chromosome inactivated, this should lead to a lower incidence of synovial sarcoma in women than in men ***(Bu et al., 2002)***.

Germline mutations in the KIT oncogene are found in patients with familial gastrointestinal stromal tumor syndrome ***(Hirota et al., 1998; Nishida et al., 1998).***

Activating KIT mutations have been shown to lead to ligand-independent activation of the KIT receptor tyrosine kinase pathway, which results in dysregulated cell growth, and are thought to be the first step in the pathogenesis of GISTs ***(Hirota et al., 1998).*** Interestingly, the identification of the important role of KIT in the pathogenesis of GISTs has led to treatment with imatinib mesylate, a small molecule drug specifically inhibits the KIT pathway ***(Demetri, 2002).***

Li-Fraumeni syndrome is a cancer syndrome where young individuals carry a substantial risk of developing sarcoma, leukemia, breast cancer, lung cancer, and adrenal tumors. Cancer incidence was studied in p53 mutation carriers >20 years of age the result showed a >100-fold higher risk of sarcoma, female breast cancer, and hematologic malignancies for the p53 mutation carriers ***(Hwang et al. 2003).***

Sarcoma subtypes and skeletal sarcoma was related to occupational risk factors in a case control study conducted among US men 1984–1988 ***(Hoppin et al. 1999).***

In a study comparing occupational risk factors for selected cancers among African American and White men in the United States, significantly increased risks were seen for exposures only in African American men, chromium exposure was associated with non-Hodgkin's lymphoma, while wood dust exposure was associated with Hodgkin's disease and Soft tissue sarcomas. The results could imply that racial disparities in levels of exposure to occupational carcinogens exist or alternatively be chance findings as confidence intervals still are broad ***(Briggs et al. 2003).***

The possibility that pesticide exposure may increase the sarcoma risk in the offspring was studied in Sweden by linking records of male pesticide applicators to the Multigeneration Register and to the Cancer Registry ***(Rodvall et al. 2003).***

Patients with Dupuytren´s contracture have an increased risk of developing Soft Tissue Sarcoma. To study the association 18 patients with the contracture who later (+5 years) developed a sarcoma were compared with other patients who did not develop a sarcoma ***(Wilbrand et al., 2002).***

Approximately half of all Soft Tissue Sarcoma patients with intermediate or high-grade tumors develop metastatic disease requiring systemic treatment ***(Coindre et al., 2001)*** and the overall survival is approximately 50% at 5 years ***(Kotilingam et al., 2006).***

Types of Soft Tissue Sarcoma

The histological classification of soft tissue tumors used reflects the World Health Organization (WHO) classification adopted in 2002. This classification includes a revised categorization of biological behavior that now allows for two designations of intermediate malignancy: locally aggressive and rarely metastasizing ***(Christopher et al., 2002)***.

TABLE 1 World Health Organization classification of soft tissue tumors **(*Kleihues and Cavenee, 2000; Christopher et al., 2002; Miettinen, 2003*)**

Adipocytic Tumors	**Intermediate (Rarely Metastasizing)**	**Vascular Tumors**
Benign	Solitary fibrous	Hemangiomas
Lipoma	tumor and	Epithelioid hemangioma
Lipomatosis	hemangiopericytom	Angiomatosis
Lipomatosis of nerve	a	Lymphangioma
Lipoblastoma/lipoblastomato	Inflammatory	**Intermediate (Locally**
sis	myofibroblastic	**Aggressive)**
Angiolipoma	tumor	Kaposiform
Myolipoma of soft tissue	Low-grade	hemangioendothelioma
Chondroid lipoma	myofibroblastic	**Intermediate (Rarely**
Spindle cell	sarcoma	**Metastasizing)**
lipoma/pleomorphic lipoma	Myxoinflammatory	Retiform hemangioendothelioma
Hibernoma	fibroblastic sarcoma	Papillary intralymphatic
Intermediate (Locally	Infantile	angioendothelioma
Aggressive)	fibrosarcoma	Composite hemangioendothelioma
Atypical lipomatous	**Malignant**	Kaposi sarcoma
tumor/well-differentiated	Adult fibrosarcoma	**Malignant**
liposarcoma	Myxofibrosarcoma	Epithelioid hemangioendothelioma
Malignant	Low-grade	Angiosarcoma of soft tissue
Dedifferentiated liposarcoma	fibromyxoid	**Chondro-Osseous Tumors**
Myxoid liposarcoma	sarcoma	Soft tissue chondroma
Round cell liposarcoma	Sclerosing	Mesenchymal chondrosarcoma
Pleomorphic liposarcoma	epithelioid	Extraskeletal osteosarcoma
Mixed-type liposarcoma	fibrosarcoma	**Tumors of Uncertain**
Liposarcoma, not otherwise	**So-called**	**Differentiation**
specified	**Fibrohistiocytic**	**Benign**
Fibroblastic/Myofibroblasti	**Tumors**	Intramuscular myxoma
c Tumors	**Benign**	Juxta-articular myxoma
Benign	Giant cell tumor of	Deep â€œaggressiveâ€
Nodular fasciitis	tendon sheath	angiomyxoma
Proliferative fasciitis	Diffuse-type giant	Pleomorphic hyalinizing
Proliferative myositis	cell tumor	angiectatic tumor of soft parts
Myositis ossificans and	Deep benign fibrous	Ectopic hamartomatous thymoma
fibroosseous pseudotumor of	histiocytoma	**Intermediate (Rarely**
digits	**Intermediate**	**Metastasizing)**
Ischemic fasciitis	**(Rarely**	Angiomatoid fibrous histiocytoma

Elastofibroma
Fibrous hamartoma of infancy
Myofibroma/myofibromatosis
Fibromatosis coli
Juvenile hyaline fibromatosis
Inclusion body fibromatosis
Fibroma of tendon sheath
Desmoplastic fibroblastoma
Mammary-type myofibroblastoma
Calcifying aponeurotic fibroma
Angiomyofibroblastoma
Cellular angiofibroma
Nuchal-type fibroma
Gardner fibroma
Calcifying fibrous tumor
Giant cell angiofibroma

Intermediate (Locally Aggressive)

Superficial fibromatosis
Desmoid-type fibromatosis
Lipofibromatosis

Metastasizing)

Plexiform fibrohistiocytic tumor
Giant cell tumor of soft tissue

Malignant

Pleomorphic MFH/undifferentiated pleomorphic sarcoma
Giant cell MFH/undifferentiated pleumorphic sarcoma with giant cells
Inflammatory MFH/undifferentiated pleomorphic sarcoma with prominent inflammation

Smooth Muscle Tumors

Benign

Angioleiomyoma
Deep leiomyoma
Genital leiomyoma

Malignant

Leiomyosarcoma

Pericytic (Perivascular) Tumors

Glomus tumor
Myopericytoma

Skeletal Muscle Tumors

Benign

Rhabdomyoma

Malignant

Embryonal rhabdomyosarcoma
Alveolar rhabdomyosarcoma
Pleomorphic rhabdomyosarcoma
Ossifying fibromyxoid tumor
Mixed tumor/myoepithelioma/parachordoma

Malignant

Synovial sarcoma
Epithelioid sarcoma
Alveolar soft part sarcoma
Clear cell sarcoma of soft tissue
Extraskeletal myxoid chondrosarcoma
PNET/extraskeletal Ewing tumor
Desmoplastic small round cell tumor
Extrarenal rhabdoid tumor
Malignant mesenchymoma
Neoplasms with perivascular epithelioid cell differentiation (PEComa)
Intimal sarcoma

PERIPHERAL NERVE SHEATH TUMORS

Nonneoplastic Lesions

Morton neuroma
Traumatic neuroma

Neurofibroma

Cutaneous
Cellular
Diffuse
Epithelioid

Schwannoma

Conventional
Cellular
Plexiform
Epithelioid

Nerve Sheath Myxoma

Perineurioma

Intraneural perineurioma
Soft tissue perineurioma

Granular Cell Tumor

Granular cell tumor
Malignant granular cell tumor

Malignant Peripheral Nerve Sheath Tumor (MPNST)

Malignant peripheral nerve sheath tumor
MPNST with rhabdomyoblastic differentiation

PNET, primitive neuroectodermal tumor.

Malignant Fibrous Histocytoma (undifferentiated pleomorphic sarcoma)

Malignant fibrous histiocytoma (MFH) occurs usually in the extremities and was considered as the most common soft tissue tumor in older adults. It is a heterogeneous pathological entity with several histological subtypes (storiform-pleomorphic, giant cell and inflammatory) and presumably derived from histiocytes that are capable of fibroblastic transformation ***(Erlandson and Antonescu, 2004)***.

There are controversial opinions about its pathogenesis and the validity as a clinicopathological entity ***(Randall et al., 2004)***, however a small subset (< 3%) arises at the site of prior radiation therapy and rarely at the site of chronic ulceration. A case of MFH and squamous carcinoma that derived from an old burn scar was reported ***(Ozercan et al., 2004)***. Clinicopathologic, ultrascructural and immunohistochemical studies have shown that malignant fibrous histiocytomas are not derived from histiocytic "facultative fibroblasts" and many neoplasms so diagnosed actually are pleomorphic subtypes of other sarcomas ***(Erlandson and Antonescu, 2004)***. The actual WHO-Classification uses undifferentiated pleomorphic sarcoma NOS (not otherwise specified) synonymously. Also the myxoid variant of MFH is now called myxofibrosarcoma and remains as distinctive and discrete entity ***(Fletcher et al., 2002)***.

It occurs rarely in childhood and the incidence increases with age. Most of the patients are at the age of over 40 with a peak in the 6th and 7th decade. Approximately two thirds are men, and Whites are affected more often than Blacks or Asiens. Clinical features are similar for all MFH subtypes, therefore they are being described together. The tumor occurs as a painless, enlarging mass that grows over several months and is most frequently located on the extremities and on the retroperitoneum. The majority of cases arise in subfascial soft tissue, while less than 10% are primarily subcutaneous. Around 5% of the patients have metastases at presentation, most often to the lung (***Enzinger and Weiss, 1988).***

Liposarcoma

Liposarcoma is one of the most frequent malignant soft tissue tumors and currently classified into five main subgroups: well-differentiated, myxoid, round cell, pleomorphic, and dedifferentiated ***(Fletcher et al., 2002)***. Well-differentiated liposarcoma is the most common subtype of liposarcoma, representing approximately half of all