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Risk assessment of radio-chemotherapy in pediatric soft tissue sarcomas

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ABSTRACT

Soft tissue sarcomas (STS) are a group of rare and heterogenous cancers, that diverse a wide spectrum of histology and varied clinical behavior. The aim was to study, retrospectively and prospectively the adverse effects of therapy in STS patients attending the Pediatric Oncology Clinic, National Cancer Institute (NCI), Cairo University during the last 10 years. Files of 106 STS patients were revised for history, staging, investigations, treatment modalities and side effects of therapy. Radiotherapy (RTH) and surgery remains the backbone of the multi-modality treatment plan. Chemo-radiotherapy (CRTH) induces acute and delayed toxicity in the form of hematological & gastrointestinal (GIT) toxicity and alopecia that occur in all patients. However, hepatic & genitourinary toxicity, cardiotoxicity, neurotoxicity and skin complications can be seen in 13.2%, 11.3%, 1.9% and 4.7% and 28.3% of patients respectively. Mucositis was noticed in 42.5% of patients, 15.1% of them were due to RTH, which can also cause dysphagia & dysphonia, impaired taste sensation and transient conjunctivitis in 4.7%, 1.9% and 6.6% of patients respectively. Additionally, 46.7% of post-pubertal patients were found to be azoospermic >5 years of end of treatments. However, 3.8% and 6.6% of patients developed ototoxicity and skin fibroses due to local irradiations. Furthermore, hypo- or hyperthyroidism and growth retardation was encountered in 7.5% and 6.6% of patients respectively. However, 5.7% of patients developed secondary malignancy, 7 years after the end of CRTH.

Finally, the current study concluded that STS multidisciplinary management may cause early and late toxicity. Future approaches including radiation dose and volume reduction or application of new radiation technologies are needed. New strategies with reduction or elimination of chemotherapy (CTH) dose are also recommended for dealing with pediatric STS patients.

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1. Introduction

Soft tissue sarcoma (STS) constitutes a heterogenous group of rare cancers, with heterogenous clinical presentation, histological subtypes and molecular alterations (Blay et al., 2013). Therefore, its management requires an experienced multidisciplinary team in an expert center (Faivre, & Le Péchoux, 2013). They constitute about 1% of all solid tumors, (Shukla & Deo, 2011) and can occur in any part of the body (Umer, Umer, Qadir, Abbasi, and Masood, 2013). It present most commonly as an asymptomatic mass, and swelling was the presenting symptom in 96% patients (Shukla & Deo, 2011). Their biological behavior is characterized by local aggressiveness and tendency to hematogenous spreading. Almost 50% of STS patients develop metastatic disease, mainly within three years from initial diagnosis. The distribution of metastases from STS varies, depending on the primary site and histological subtype (Vincenzi et al., 2013). The prognosis of STS is determined by histological subtype, tumor size, localization, grade and the presence of metastases (Jakob, Rauch, Wenz, and Hohenberger, 2013). In pediatric oncology, most treatment concepts in the 21st century are of curative intent, aiming at long-term overall survival (OS) (Combs et al., 2012). The goals of sarcoma management include both a cure and functional preservation of involved tissues and adjacent critical structures (Kandel et al., 2013). With the advances made in the fields of imaging, surgical, medical and radiation oncology along with better understanding of tumor pathology and biology more effective management protocols are currently available (Shukla & Deo, 2011). Treatment are often multimodal and complex, and patients can experience significant morbidity and mortality as a consequence of treatment or the disease (Kandel et al., 2013). The standard treatment protocol involves wide surgical resection along with neoadjuvant or adjuvant RTH (Umer et al., 2013). The mainstay of therapy of non-metastasized STS is complete surgical resection combined with irradiation in large, high-grade tumors which are located deep to the superficial body fascia (Jakob et al., 2013). The application of brachytherapy (BRT) as a complementary therapy in STS has a history of 30-years. BRT seems to be a good method of adjuvant therapy in extremity STS, however its accessibility is limited. The number of complications was small. Further multicentre randomized studies should decide which method of adjuvant treatment (external beam radiation therapy (EBRT) vs. BRT) is better and what is the optimal sequence of therapies improving local control (Guzik, Lyczek, and Kowalik, 2012). The established standard of care for unresectable STS in first line is doxorubicin-based CTH, with typical response rates ranging from 10% to 30%. For patients who relapse or develop resistance, other therapeutic options were limited before the availability of trabectedin. For these patients, progression-free survival (PFS) and OS rarely exceed 6 months and 1 year respectively (Blay et al., 2013).

With continuous increase in tumor control and cure, also side effects of the treatments, especially long-term side effects, have moved even more into focus (Combs et al., 2012). Examples are cardiac toxicity from anthracyclines, hearing loss or tinnitus from cisplatin, infertility from alkylator therapy or radiation to the pelvis, endocrine complications usually from radiation to reproductive organs or the hypothalamic-pituitary axis, bladder dysfunction from CTH and radiation, and second malignant neoplasms due to radiation and/or CTH (Arndt, Rose, Folpe, and Laack, 2012; Ginsberg, Goodman, and Leisenring, 2010; Nagarajan, Kamruzzaman, and Ness, 2011). Furthermore, thrombocytopenia (TCP) is a common side effect of CTH, and multiple studies have suggested that Chemotherapy-induced thrombocytopenia (CIT) is a dose-limiting adverse event (AE) in the treatment of cancer, and can necessitate dose delays and/or dose reductions (Chawla et al., 2013). On the other hand, children receiving platinum-compound CTH for the treatment of malignancies may be at risk of an early- or delayed-onset hearing impairment that may affect learning, development, communication, school performance, social interaction and overall quality of life (Nitz et al., 2013; Orgel et al., 2012; PecoraLiberman et al., 2011; Skinner, 2004). However, port-associated complications (paravasation, irritation, infection) were more frequent (13%) than in continuous infusion protocols with other drugs (e.g., 5-FU) administered in the large outpatient center (Hoiczyk et al., 2013). With respect to RTH, sparing of normal tissue and reduction of integral dose is the most effective means to prevent treatment-related side effects. Over the last decades, advances in radiation oncology from conventional 2D-to 3D-radiation therapy, to the establishment of high-precision stereotactic RTH and subsequently intensity-modulated radiotherapy (IMRT) have continuously enabled the radiation oncologist to deliver higher local doses even to complex target volumes while sparing surrounding organs at risk (OAR). However, intermediate and low doses of radiation remain to be applied. One way of reducing integral dose and potentially reducing side effects is the use of particle therapy, due to the physical properties of ion beams (Combs et al., 2012). Although the introduction of multimodal treatment of STS improved local tumor control, local failure still occurs in a good number of patients. Therefore, further improvement of current treatment strategies is necessary (Jakob et al., 2013).

The aim of the present work is to retrospectively and prospectively study the adverse effects of therapy in STS patients attending the Pediatric Oncology Clinic, National Cancer Institute (NCI), Cairo University during the last 10 years (from January 2004 till January 2014).

2. Patients and methods

One hundred and six STS patients were recorded among the total pediatric malignant cases registered during the period of study. Data were collected about age of the patients at presentation, sex, primary site (s), staging, histopathological subtype, site of metastases (if present) and dose & duration of therapy. Clinical examinations were done laying stress on site and clinical extent of tumor with assessment of nodal enlargement. Results of routine laboratory investigations; bone marrow aspiration and/or biopsy were also reviewed. The results of plain X-ray, CT scans or MRI, isotopic bone scan for evaluations of the primary site and metastasis. Scrotal sonography for paratesticular tumor was also identified. Urinalysis and assessment of bladder function by cystourethrogram in case of hemorrhagic cystitis. Follow-up was