Considerations for the Long Term Treatment of Pediatric Sarcoma Survivors

Abstract

Sarcomas are primary malignancies of the connective tissues. They are exceedingly rare in adults, but much more common in children. The historically recent advent of cytotoxic chemotherapy for pediatric sarcomas has revolutionized the treatment of these diseases and dramatically improved their prognoses. There is thus a population of pediatric sarcoma survivors that are "coming of age" as adults. However, this progress is not without consequences. Due to aggressive treatment protocols that include various combinations of surgery, chemotherapy, and radiation therapy, pediatric sarcoma survivors are at risk of myriad physical, medical, and psychological difficulties as they enter adulthood. These include but are not limited to physical disabilities, chemotherapy-induced cardiac issues, second malignancies, and anxiety. These patients pose unique challenges to their adult primary care physicians. One possible solution to these challenges is multidisciplinary sarcoma survivorship clinics. By paying greater attention to the unique issues of pediatric sarcoma survivors, involved physicians can maximize the physical and emotional health of pediatric sarcoma survivors.

Keywords: *Cancer, preventative, sarcoma, survivorship*
MeSH terms: *Sarcoma, paediatrics, paediatric psychology, cancer chemotherapy protocols*

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Introduction

Sarcomas are a rare group of tumors that represent <1%–2% of all adult malignancies. However, they are much more common in younger patients. In a recent study of over 10,000 American pediatric cancer survivors, nearly 17% were sarcoma survivors.[1] The combination of aggressive treatment with anthracycline-based chemotherapy, radiation therapy, and surgery makes sarcoma survivors uniquely susceptible to long term treatment complications. Among these are cardiotoxicity, musculoskeletal dysfunction, second malignancies, and myriad medical, surgical, and psychological issues.[2-4] The first part of this article will review some of the common long term complications faced by sarcoma survivors. The second part will explore the emerging concept of sarcoma survivorship, its inherent challenges, and how sarcoma survivorship clinics may provide a valuable service for this subset of patients.

Part 1 - Background and Long Term Complications of Sarcoma Treatment

Sarcomas encompass a heterogeneous group of malignant neoplasms that arise in tissues of mesenchymal origin. Among these, the most commonly arise from bone (osteosarcoma), fat (liposarcoma), and cartilage (chondrosarcoma). While sarcomas as a whole are rare diseases (only 1%–2% of human malignancy), they are much more common in children, where they are the third most common form of cancer. Among this latter group, osteosarcoma, Ewing sarcoma, and rhabdomyosarcoma are predominate.

Before the chemotherapeutic era, sarcoma survivors were rare. For example, the survival of patients with osteosarcoma and Ewing sarcoma (the first and second most common sarcomas of bone, respectively) was an abysmal 10%–20%. With the advent of modern treatment strategies that employ chemotherapy, surgery, and radiation therapy, the expected 5-year survival for both of these diseases now hovers around 70%. Therefore, although sarcoma survivors are still a small community, they are a larger community than at any time in history. It is thus prudent to understand the sequelae that are inherent to the aggressive treatments that have become the standards of care in sarcoma treatment. In fact, in a recent large series of pediatric cancer survivors, the Children's Cancer Survivorship Study found more evidence

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of chronic illness in sarcoma survivors than in survivors of other pediatric cancers.[4] Another study from the British Columbia Cancer Agency demonstrated that 77% of Ewing sarcoma survivors experienced some form of long term complication.[3]

Chemotherapy-induced Cardiotoxicity

The anthracycline chemotherapy doxorubicin (adriamycin) is ubiquitous in the medical oncologic treatment of sarcomas. We, therefore, address the issues surrounding this drug specifically and in some detail. Other chemotherapeutic agents have been transient and/or recent additions to sarcoma medical management and are not as well studied. Doxorubicin is a DNA intercalator, causing rapidly dividing cells to undergo apoptosis. Undoubtedly, the use of doxorubicin has helped to improve the prognosis of sarcoma patients. However, this improvement is not without cost. Cardiotoxicity is a known complication of doxorubicin. This is thought to be mediated by free radical-induced myocyte injury. The consequences of this are decreased ventricular wall thickness, increased afterload, and decreased contractility. Although 450 mg/m^2 was previously considered the threshold dose for cardiotoxicity, recent data suggest that risk is elevated after 200–250 mg/m^2, and the severity of cardiotoxicity seems to increase in a dose-dependent fashion.[4] This irreversible cardiotoxicity is perhaps the most alarming medical issue that confronts sarcoma survivors.[1]

In their series of 101 Ewing sarcoma survivors treated at the British Columbia Cancer Agency, Hamilton *et al*. reported that 28% of their patients exhibited signs of cardiotoxicity. Among these patients, 18 had severe dysfunction, 1 required a pacemaker, 2 underwent heart transplant, and 3 died from cardiac pathology.[3]

Sarcoma survivors may have reduced life expectancy and signs of heart disease in their 30s and 40s. In their comprehensive review of pediatric cancer survivorship, the authors noted that acquired heart disease in a 30-year-old is rare, but heart disease in a 30-year-old sarcoma survivor is not.[1]

Musculoskeletal Problems

Besides cytotoxic chemotherapy, the treatment of sarcoma nearly always requires aggressive surgery in all patients and frequently requires radiation therapy, especially in the adult population. These modalities, while essential for local control, can leave the patient with lifelong musculoskeletal dysfunction. As sarcomas are, by definition, diseases of the connective tissues, sarcoma survivors are uniquely vulnerable to these long term sequelae. In their review of Ewing sarcoma survivors from their institution, Hamilton *et al*. found that 50% of their patients experienced musculoskeletal abnormalities.[3] Radiation-induced bone and soft tissue insufficiency can emerge over years. Musculoskeletal sequelae of radiation include diminished wound healing, atrophy, fibrosis, edema, osteopenia, decreased motion, chronic pain, and pathological fracture.[4] The functional impairments caused by surgery are accentuated by radiation doses of 30–60 Gy. The physes (growth plates) of skeletally immature patients are particularly sensitive to external beam radiotherapy, with linear growth arrest seen at radiation doses as low as 10–20 Gy.[4]

Psychosocial Issues

Taking this even further, Gerrand and Furtado drew attention to the psychological and social difficulties faced by sarcoma survivors.[5] They reported psychological stress in approximately a third of patients. Understandably, anxiety was common at the time of diagnosis, whereas depression was a later finding.[5] Patients also experienced psychological stress related to amputation and alterations in body image. Socially, sarcoma affects patients' relationships, as well as physical intimacy. Physical fitness can be complicated and difficult for sarcoma survivors due to sequelae from surgery. Survivors may need to alter recreational activities to include different sports or different levels of engagement. It is encouraging that patients with amputations and limb-sparing surgery participate in sports at similar rates, but physical fitness and the resultant positive social effects of sports are undoubtedly challenging for all survivors of musculoskeletal malignancies.

Other Issues

Besides the aforementioned complications, sarcoma survivors are at risk for a host of other medical problems that are consequences of chemotherapy, radiation, surgery, or a combination of these. Sarcoma survivors are at a substantially increased risk of developing chronic illnesses including heart disease, diabetes, hypertension, dyslipidemia, kidney failure, obesity, psychological problems, and second malignancies.[6,7] In fact, the Children's Cancer Survivorship Study found that the incidences of chronic illness were much higher in sarcoma survivors than the survivors of other pediatric malignancies.[1] The British Columbia Cancer Agency study demonstrated that the incidence of a second neoplasm among Ewing sarcoma survivors was 5% at 10 years and 23% at 20 years.[3] In this group of sarcoma survivors, there were 11 secondary neoplasms in eight patients at a median of 18.3 years after diagnosis. It is worth noting that all of these were in patients who had received radiation, and most of them were "in-field" secondary malignancies.[3] The previous diagnosis of sarcoma was an independent risk factor for the development of a second neoplasm, according to the review by Harrison and Schwartz at the University of Texas MD Anderson Cancer Center.[4] They also found that radiation predisposes to melanoma and other skin cancers, thyroid cancer, breast cancer, and other sarcomas. They further

reported that in-field radiation-induced sarcomas typically occurred 10 years after treatment.[4]

Nonmusculoskeletal sequelae of radiation also include endocrinopathy, infertility, bowel obstruction, diarrhea, cataracts, dental problems, sinus problems, hearing loss, and lung disease.[4] Radiation-induced nephropathy occurs at doses over 20–25 Gy but can occur at lower doses if the patient receives simultaneous chemotherapy. After a dose of 40 Gy, bladder dysfunction can occur with an incidence of 27%, which can also be enhanced by concomitant chemotherapy.[4]

Newer sarcoma chemotherapy protocols prescribe ifosfamide in addition to doxorubicin. This can cause short and long term renal damage including proximal tubular damage, hyperphosphaturia, glycosuria, aminoaciduria, Fanconi Syndrome, persistent hypophosphatemia, and nephrogenic rickets.[4] Ifosfamide and cyclophosphamide can also lead to long term fertility complications including azoospermia in male patients. Ifosfamide-induced gonadotoxicity seems to occur at doses over 60 g/m^2.[4] Ifosfamide treatment also predisposes to leukemia as a second malignancy.

Part II - Challenges and Potential Solutions of Sarcoma Survivorship

Given the complexity of sarcoma treatment and the impressive catalog of potential long term issues, it is not shocking that a 2014 manuscript by Suh and Daugherty reported that internists are generally uncomfortable treating the survivors of childhood cancer.[8] This is only part of a multifactorial process that keeps sarcoma survivors from receiving appropriate long term care. Patients may not be well informed regarding their need for long term surveillance or their unique susceptibility to chronic medical problems.[2] Older survivors no longer feel comfortable seeing their pediatric oncologists, who are also unfamiliar with the treatment of chronic adult medical problems. Surgeons may be the only practitioners who continue to see the patient regularly but are also not well equipped to address chronic medical issues. All of these factors contribute to the benign neglect of sarcoma survivors. The American Society of Clinical Oncology has published guidelines on the care of breast, prostate, and colon cancer survivors, but these are unlikely to adequately address the physical needs of sarcoma survivors.[2,9]

To address the demands of this clearly unmet need, sarcoma medical oncologist[2] established Sarcoma Survivorship Clinics.[2] Patients aged 16 and older who have been off of treatment for 2 years are eligible to participate. The goal of this highly specialized clinics is to address the long term medical and psychological needs of sarcoma survivors, with a holistic approach and a strong emphasis on preventive medicine.[2] Yearly patient-specific surveillance visits characterize each survivor's personal risk profile based on treatment history, genetic predisposition, lifestyle, and other comorbidities.[2]

During the typical survivorship clinic visit, a specific checklist is completed to address the needs of each patient. Patients receive a chest X-ray to ensure that there is no radiographic evidence of metastatic disease. Given the ubiquity of doxorubicin-induced cardiotoxicity, there is a strong focus on screening for cardiovascular health. All sarcoma survivors who received doxorubicin undergo an echocardiogram with strain. Survivors are also comprehensively screened for musculoskeletal dysfunction, metabolic anomalies, diabetes, hypertension, coronary artery disease, anxiety, depression, renal insufficiency, and obesity.[2] In addition to these measures, sarcoma survivors perform a 6 min walk and meet with a dietician to evaluate physical fitness and encourage healthy nutritional habits. Finally, the survivors fill out National Institutes of Health Patient Reported Outcome Measurement Information System surveys in the domains of anxiety, depression, mobility, pain interference, sleep disturbance, and physical function.[2] The outcomes of these surveys may prompt additional treatments or referrals. Treatment plans generated from each survivorship encounter are subsequently shared with the survivor's primary care doctor. This helps the primary doctor both understand the importance of the survivorship clinic and empowers him/her to become an active participant in the process.

Conclusions

The treatment of sarcoma patients requires aggressive, personalized oncologic strategies that are fraught with potential long term consequences. Therefore, it is not surprising that the long term care of sarcoma survivors is also challenging and requires careful attention to the issues experienced by this unique subset of cancer survivors. Among these are cardiovascular disease, musculoskeletal dysfunction, and other potential problems as outlined above. It has been our intent to highlight some of these unique challenges and clearly illustrate that more and better research in this area is essential to better serve sarcoma survivors.

A recent and inventive solution is the establishment of Sarcoma Survivorship Clinics modeled after the University of Michigan's protocol. These could potentially address the specific long term preventative care needs of sarcoma patients and perhaps de-mystify the unique challenges posed by this small but growing group of cancer survivors. This offers an intriguing model for other sarcoma treatment centers to emulate.

As Maya Angelou wrote, "Surviving is important, thriving is elegant." It is our hope that improved attention to the long term care of sarcoma patients will allow them to survive and thrive despite the aggressiveness of their treatment protocols.

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Dr. Weiss is an osteosarcoma survivor who was treated with chemotherapy, experimental muramyl tripeptide-phosphatidylethanolamine, and surgery. He is a transfemoral amputee. Dr. Zimel is a Ewing sarcoma survivor who was treated with chemotherapy, external beam radiotherapy, and surgery. She has a complex pelvic reconstruction. Drs. Weiss and Zimel are both active members of the Musculoskeletal Tumor Society. They wish to thank Dr. Laurence Baker, MD at the University of Michigan for his foundational contributions to the research and treatment of sarcoma survivorship.

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Conflicts of interest

There are no conflicts of interest.

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