

REVIEW ARTICLE

Cardiovascular and Oncological Aspects of Chemotherapy in Patients with Locally Advanced Soft Tissue Sarcomas

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Abstract

Background: Soft tissue sarcomas (STS) are a heterogeneous group of rare malignant tumors that require individualized multimodal treatment. Anthracyclines, particularly doxorubicin, remain a cornerstone of systemic therapy; however, their use is associated with a clinically important risk of cardiotoxicity, especially at high cumulative doses.

Objective: This article reviews the cardiovascular effects of systemic therapies used in patients with locally advanced and metastatic STS, with particular emphasis on anthracycline-associated cardiotoxicity, its risk factors, prevention, monitoring, and long-term cardiovascular outcomes.

Methods: The article discusses available clinical evidence regarding anthracycline-based chemotherapy and other systemic treatment modalities used in STS, including tyrosine kinase inhibitors, alternative cytotoxic agents, and immune checkpoint inhibitors. Current approaches to cardiovascular risk assessment, prevention, monitoring, and survivorship care are also reviewed.

Results: Anthracycline-associated cardiac dysfunction represents an important treatment-related complication in patients with STS, particularly in those receiving high cumulative doses. Continuous infusion, dexrazoxane, liposomal formulations, cardiovascular risk-factor management, and appropriate cardiac monitoring may reduce the risk of cardiotoxicity. Other systemic therapies may cause distinct cardiovascular complications, including arterial hypertension, left ventricular dysfunction, QTc prolongation, thromboembolic events, and immune-mediated myocarditis.

Conclusion: Cardiovascular risk assessment and monitoring should be integrated into the management of patients with STS from the initiation of systemic therapy through long-term survivorship. A multidisciplinary cardio-oncology approach may facilitate early detection and management of treatment-related cardiovascular complications while allowing effective oncological therapy to continue.

Keywords: Anthracyclines, Soft tissue sarcoma, Chemotherapy complications, Tyrosine kinase inhibitors

Introduction

Sarcomas constitute a heterogeneous group of rare neoplasms arising from connective tissue. These tumors account for approximately 1% of newly diagnosed oncological diseases in adults and about 15% of malignant neoplasms in children each year. Based on the identification of more than one hundred histological subtypes, sarcomas are classified into soft tissue (approximately 80%) and bone (approximately 20%) origins.

Each histological subtype is characterized by specific clinical and anatomical features, metastatic potential, and biological behavior. This heterogeneity creates significant challenges in diagnostic and therapeutic approaches. At the same time, the limited availability of high-quality

prospective data on rare tumors represents one of the key factors hindering the standardization of clinical practice.

According to the American Cancer Society (2024), approximately 13,400 new cases of soft tissue sarcoma (STS) are diagnosed annually. Although the median age at diagnosis is 61 years, this parameter varies across different histological subtypes. STS most commonly arises in the extremities; less frequently, it involves the trunk, retroperitoneal space, and visceral organs, and least commonly the head and neck region.

The treatment strategy for STS is individualized based on factors such as histological subtype, tumor grade, size, metastatic status, and anatomical location. In most cases,

multimodal approaches combining surgery, radiotherapy, and systemic therapy are employed. Systemic therapy typically includes the use of anthracyclines as monotherapy or in combination regimens, followed by other cytotoxic chemotherapeutic agents, targeted therapies, and immunotherapy in subsequent lines of treatment.

Molecular profiling has led to significant advances in understanding the biological basis of oncologic diseases, including sarcomas. In particular, fluorescence in situ hybridization and next-generation sequencing technologies play a key role in the diagnosis of Ewing sarcoma, synovial sarcoma, and gastrointestinal stromal tumors (GIST). These molecular approaches have contributed to improved clinical outcomes through the use of tyrosine kinase inhibitors (TKIs) in GIST, as well as immunotherapy in undifferentiated pleomorphic sarcoma and cutaneous angiosarcoma.

Nevertheless, the treatment of locally advanced and metastatic sarcomas still largely relies on conventional cytotoxic chemotherapy regimens. Although agents such as trabectedin, dacarbazine, and eribulin have led to certain advances, the development of resistance to these drugs remains inevitable. New therapeutic strategies, including tyrosine kinase inhibitors and immunotherapy, are currently under active investigation and development. However, until these approaches are fully integrated into routine clinical practice and established as first-line therapies, oncologists treating sarcoma patients continue to rely primarily on older and more toxic regimens, particularly anthracycline-based chemotherapy.

Although many treatment-related adverse effects in patients with soft tissue sarcomas (STS) can be managed with supportive care, cardiotoxicity associated with anthracycline-based regimens—especially at high cumulative doses—requires particular clinical attention. Regular cardiac assessment, including echocardiography and the use of biomarkers such as troponins and B-type natriuretic peptide, is recommended as a key component in monitoring patients receiving anthracyclines and other potentially cardiotoxic agents.

This article analyzes the impact of both soft tissue sarcomas and the systemic therapies used in their treatment on the cardiovascular system. Particular emphasis is placed on the use of anthracyclines and their cardiotoxic potential, given the high reliance on this class of drugs in clinical practice.

The Role of Anthracyclines in the Treatment of Sarcomas

Anthracyclines have long been considered a cornerstone of systemic therapy for sarcomas. Several fundamental principles have been established regarding their use. Therapeutic efficacy is dose-dependent, and doses below 60 mg/m² administered every 3 weeks are considered suboptimal. The key pharmacokinetic parameter determining

efficacy is peak plasma concentration rather than duration of exposure; therefore, administration of higher doses at 3-week intervals is accepted as the standard approach. Combination chemotherapy regimens are associated with higher response rates and improved disease-free survival (DFS) compared with anthracycline monotherapy. Among anthracyclines, doxorubicin remains the most widely used agent in the treatment of sarcomas, while epirubicin has been more extensively studied and utilized in Europe.

In patients with locally advanced soft tissue sarcoma (STS), first-line systemic therapy is based on the administration of doxorubicin at a dose of 75 mg/m² every 3 weeks, for a total of 6 cycles. Several randomized phase III trials have compared combination regimens, primarily with high-dose ifosfamide or its analogs, to doxorubicin monotherapy. Although results demonstrate higher response rates with combination approaches (approximately 25–30% vs. 5–10%), no statistically significant improvement in overall survival has been observed. Therefore, the choice between doxorubicin monotherapy and combination therapy with high-dose ifosfamide as first-line treatment remains controversial.

The evaluation of overall survival in the first-line setting is complex, as this parameter is significantly influenced by subsequent lines of therapy and the natural history of different STS subtypes included in clinical trials. As a result, the formation of heterogeneous patient populations complicates the interpretation of outcomes.

Nevertheless, in advanced leiomyosarcoma (LMS), the combination approach has gained broader acceptance based on the results of the LMS-04 study. In this trial, the addition of trabectedin to doxorubicin resulted in a significant improvement in overall survival compared with doxorubicin alone (33.1 vs. 23.8 months). For STS, including LMS, another alternative combination regimen is the use of doxorubicin with dacarbazine. However, the available evidence supporting this approach is primarily based on retrospective studies and is not sufficiently supported by high-level evidence.

The role of adjuvant chemotherapy in the treatment of soft tissue sarcomas (STS) remains controversial; however, when applied, the inclusion of high-dose anthracyclines in the regimen is considered an almost universal approach. According to one of the major meta-analyses, the most pronounced overall survival benefit was observed in patients treated with the combination of doxorubicin and ifosfamide.

Sarcoma specialists recommend the use of perioperative chemotherapy based on doxorubicin and ifosfamide in patients at high risk of recurrence, with risk stratification based on nomograms or prognostic factors such as age, tumor grade, size, resection margins, and histological subtype of STS.

In an international randomized phase III trial, histology-tailored neoadjuvant chemotherapy was compared with three cycles of an anthracycline–ifosfamide regimen in patients with localized high-risk STS. The results demonstrated that the anthracycline–ifosfamide combination significantly improved 60-month overall survival (76% vs. 66%; $P = 0.018$). Therefore, this regimen has been adopted as one of the standard treatment approaches, administered in 3–6 cycles depending on institutional protocols.

Anthracycline Rechallenge and Dose Limitations

Rechallenge or continuation of anthracyclines beyond the maximum recommended cumulative dose should be considered only in specialized centers, based on multidisciplinary team discussions and a thorough assessment of the risk–benefit balance. This approach is particularly appropriate for patients who have undergone adequate cardiological risk stratification and received preventive measures prior to initiation of anthracycline therapy.

It should be taken into account that, in most sarcoma patients, treatment strategies are designed to reach the lifetime maximum or near-maximum cumulative doses of these agents.

Anthracycline-Associated Cardiotoxicity

The principal toxic effect of anthracyclines is related to impairment of cardiomyocyte function, which ultimately leads to the development of cardiomyopathy and heart failure. In addition, other cardiotoxic effects, such as arrhythmias, may also occur and can develop independently of the primary mechanisms.

Recent evidence indicates that anthracyclines exert a damaging effect on the vascular endothelium, leading to vascular dysfunction and potentially accelerating the development of atherosclerosis, particularly in survivors who have received radiotherapy. Furthermore, an

increased incidence of arterial hypertension and metabolic disturbances has been observed in these patients.

Anthracycline-induced cardiotoxicity is classified into three main forms based on the timing of drug administration:

- Acute form — developing during or immediately after infusion.
- Early-onset chronic progressive form — occurring within the first year of treatment.
- Late-onset form — developing more than one year after treatment.

Each of these forms is characterized by specific clinical features. Acute cardiotoxicity is rare (<1%), is mainly associated with stress-related mechanisms, and is generally reversible upon discontinuation of anthracyclines.

The early-onset form is the most common clinical presentation and is typically characterized by an asymptomatic decrease in left ventricular ejection fraction (LVEF), although in some cases overt heart failure may develop. In one large cohort study, 98% of anthracycline-related cardiotoxic events occurred within the first year after completion of chemotherapy.

Late-onset cardiotoxicity is characterized by structural cardiac remodeling and leads to the development of dilated cardiomyopathy with clinical heart failure. In a large meta-analysis including 22,815 cancer patients, left ventricular dysfunction was identified in 6% of patients treated with anthracyclines, with a median time to diagnosis of 9 years. At the same time, subclinical dysfunction was detected in 18% of patients, indicating that myocardial injury represents a continuous pathophysiological process that begins at a subclinical stage and progressively evolves into overt heart failure.

The pathophysiological mechanisms of anthracycline-induced cardiotoxicity are not yet fully elucidated. Known risk factors include cumulative dose, time since exposure, age (<18 and >60 years), female sex, concomitant systemic therapies, and particularly radiotherapy directed to the mediastinum or left chest.

The development of cardiotoxicity is primarily associated with the accumulation of anthracyclines in cardiac tissue at levels exceeding the metabolic and elimination capacity of cardiomyocytes.

Recent studies suggest that the immune system may also play an important role in the pathogenesis of anthracycline-associated cardiotoxicity. In particular, neutrophils have been shown to be involved in the regulation of ferroptosis, and it is hypothesized that a reduction in neutrophils within the myocardial microenvironment may contribute to attenuation of anthracycline-induced cardiotoxicity.

Cardiovascular Outcomes in Soft Tissue Sarcoma

Data on cardiovascular outcomes associated with anthracycline exposure in patients with soft tissue sarcoma (STS) remain limited. In one retrospective study, cancer

Table 1: Anthracycline-associated cardiotoxicity: forms, risk factors, and prevention

Category	Features
Forms of cardiotoxicity	• Acute (during or immediately after infusion, <1%) • Early chronic (within the first 1 year, most common) • Late (after 1 year, dilated cardiomyopathy)
Clinical manifestations	LVEF reduction, heart failure, arrhythmias, subclinical dysfunction
Major risk factors	Cumulative dose, age (<18, >60), female gender, radiotherapy, concomitant treatments, pre-existing CV diseases
Pathogenesis	Oxidative stress, cardiomyocyte damage, ferroptosis, immune mechanisms
Monitoring methods	Echocardiography, troponin, BNP, ECG
Specific prevention	Dexrazoxane, continuous infusion, liposomal formulations
General prevention	Statins, ACE inhibitors, physical activity, smoking cessation
Clinical significance	98% of cases develop within the first year; risk of heart failure increases in the long term

therapy-related cardiac dysfunction (CTRCD) was observed in approximately 31% of STS patients. However, these figures vary significantly depending on the criteria used to define cardiotoxicity, which range from changes in left ventricular ejection fraction (LVEF) on echocardiography to the development of clinical heart failure.

For example, according to the results of the phase III ANNOUNCE trial, in patients with advanced or metastatic STS treated with doxorubicin plus olaratumab, up to 48.8% experienced either a decrease in LVEF of more than 10% from baseline or a reduction in LVEF below 50%.

The incidence of LVEF decline increased with higher cumulative doses of anthracyclines:

- 40.5% in patients receiving <450 mg/m².
- 51.6% in those receiving 450 – <600 mg/m².
- 56.2% in those receiving ≥ 600 mg/m².

At the same time, grade 3–5 cardiac dysfunction was observed in 2%, 3%, and 1.1% of cases, respectively.

In the majority of patients, cardiac adverse events developed at an early stage and were associated with high mortality. Among survivors of soft tissue sarcoma, grade 3–5 congestive heart failure was observed in 1.6% of cases, with a hazard ratio (HR) of 4.6 compared to the general population.

The relatively high incidence of cancer therapy-related cardiac dysfunction (CTRCD) in STS patients is most likely associated with the high cumulative doses of anthracyclines used in this population. In this context, risk factors are similar to those observed in other oncology patient groups and include baseline diastolic blood pressure, female sex, left ventricular end-systolic diameter, and left ventricular mass.

Strategies for the Prevention of Cardiotoxicity

Prevention of anthracycline-associated cancer therapy-related cardiac dysfunction (CTRCD) includes both specific and general cardioprotective strategies.

Specific approaches include administration of the drug as a continuous infusion, use of dexrazoxane, and application of alternative formulations such as liposomal preparations.

General cardioprotective measures include both pharmacological and non-pharmacological interventions. Pharmacological approaches involve statins and neurohormonal blockade, while non-pharmacological measures include smoking cessation, a balanced diet, and regular physical activity.

In the treatment of soft tissue sarcomas (STS), two of the most effective methods for reducing anthracycline cardiotoxicity are continuous infusion of doxorubicin and the addition of dexrazoxane. Studies conducted in various oncological patient populations have shown that, compared with bolus administration, continuous infusion of doxorubicin over up to 96 hours reduces the risk of cardiotoxicity while preserving antitumor efficacy. Dexrazoxane is considered a particularly advantageous

cardioprotective agent due to its feasibility in outpatient settings. Importantly, it does not reduce the antineoplastic efficacy of doxorubicin and is also cost-effective. Officially, dexrazoxane is recommended when the cumulative doxorubicin-equivalent dose exceeds 300 mg/m². However, in STS patients—where high cumulative doses are anticipated—its use from earlier stages of treatment is considered appropriate.

An alternative approach is to increase selective drug delivery to tumor tissue while reducing exposure to cardiac tissue. In this context, liposomal and pegylated liposomal doxorubicin demonstrate more favorable pharmacokinetic properties.

However, these formulations are more frequently associated with adverse effects such as mucositis and hand-foot syndrome, which may limit the maximum tolerated dose. Although existing studies suggest that these agents may be potentially less effective than conventional anthracyclines, direct comparison is difficult due to methodological differences, and randomized trials are lacking. In clinical practice, liposomal doxorubicin is sometimes used in patients who have exceeded the maximum cumulative dose, until disease progression or unacceptable toxicity, under close cardiological monitoring.

It is important to note that specific clinical studies on the early prevention of anthracycline-associated cardiotoxicity in patients with STS are limited. Most of the available evidence is derived from breast cancer populations treated with lower cumulative doses. However, STS patients represent a distinct high-risk group due to their exposure to higher cumulative doses, underscoring the need for further high-quality research in this area.

Results from randomized clinical trials indicate that neurohormonal blockade, including beta-blockers and inhibitors of the renin-angiotensin-aldosterone system, may attenuate the decline in left ventricular ejection fraction (LVEF) to some extent. However, these interventions do not significantly reduce the incidence of symptomatic heart failure; therefore, their use is mainly recommended in high-risk patient populations.

Although clinical outcomes are not entirely consistent, statins may also exert a potential cardioprotective effect in high-risk patients receiving anthracyclines and may be considered in this context.

Non-pharmacological interventions, particularly regular moderate-intensity physical activity, remain underutilized in the prevention of anthracycline-related cancer therapy-related cardiac dysfunction (CTRCD). However, existing evidence supports their effectiveness, and their systematic implementation before, during, and after anthracycline therapy is advisable.

Ongoing clinical trials are investigating novel cardioprotective pharmacological strategies, including

Table 2: Main therapies used in the treatment of soft tissue sarcomas and their cardiovascular effects

Type of therapy	Representative preparations	Field of use	Major cardiovascular side effects	Note
Anthracyclines	Doxorubicin, Epirubicin	First line systemic treatment	Cardiomyopathy, heart failure, decreased LVEF, arrhythmias	Dose-dependent cardiotoxicity, risk increases with high cumulative doses
Tyrosine kinase inhibitors (TKIs)	Pazopanib, Cabozantinib	Metastatic and resistant YTS	Arterial hypertension, QT prolongation, LVEF decrease, thromboembolism	Associated with VEGFR inhibition
Alternative cytotoxic drugs	Trabectedin, Gemcitabine, Eribulin, Docetaxel, ifosfamide	The next line of treatment	Heart failure, cardiomyopathy, arrhythmias (rare)	Trabectedin with higher risk of cardiotoxicity
Immunotherapy (ICI)	Pembrolizumab, Nivolumab, Ipilimumab	Selected YTS subtypes	Myocarditis, pericarditis, heart failure, MI	Myocarditis is a rare but highly fatal disease.
Liposomal anthracyclines	Pegylated doxorubicin	An alternative approach	Less cardiotoxicity	Other toxicities (mucositis, hand-foot syndrome) are possible

angiotensin receptor–neprilysin inhibitors, sodium–glucose cotransporter 2 (SGLT2) inhibitors, ranolazine, and other agents.

Non-Anthracycline Therapies in the Treatment of Soft Tissue Sarcomas

Although anthracyclines are the most extensively studied agents in terms of cardiotoxicity, many other drugs used in the treatment of sarcomas may also have significant effects on the cardiovascular system. It should be noted that anthracyclines are typically used as first-line therapy in advanced disease. Therefore, patients receiving subsequent lines of treatment may already carry an increased risk of existing or potential cardiac dysfunction due to prior anthracycline exposure.

Tyrosine Kinase Inhibitors (TKIs)

In the pivotal PALETTE trial (pazopanib vs. placebo), which included 369 patients with metastatic and chemotherapy-resistant soft tissue sarcoma (STS), pazopanib significantly improved median progression-free survival (PFS) compared with placebo (4.6 vs. 1.6 months).

Due to its approved indication across a broad spectrum of STS subtypes, excluding liposarcomas, pazopanib is frequently used in clinical practice as a later-line therapy. Pazopanib is an orally administered multi-target tyrosine kinase inhibitor (TKI) that primarily inhibits VEGFR1/2/3 receptors and, to a lesser extent, platelet-derived growth factor receptors (PDGFR) and the stem cell factor receptor (KIT), thereby suppressing tumor angiogenesis and proliferation.

This class of agents is most commonly associated with arterial hypertension; however, rare adverse effects

include left ventricular systolic dysfunction, QTc interval prolongation, and arterial or venous thromboembolic events. The pathogenesis of these effects is likely related to disruption of cardiac homeostasis due to inhibition of VEGFR and other kinases, microstructural changes in the myocardial capillary network, and dysregulation of the nitric oxide–endothelin balance. Similar to pazopanib, cabozantinib has demonstrated clinical activity in soft tissue sarcomas through its inhibitory effects on VEGFR, mesenchymal–epithelial transition factor (MET), and AXL, a receptor tyrosine kinase of the TAM family, and has been applied across various STS subtypes. This agent is also associated with arterial hypertension, and cases of cardiac dysfunction, including reductions in left ventricular ejection fraction (LVEF), have been reported. In a prospective real-world study in patients with renal cell carcinoma, cabozantinib treatment was associated with a decrease in LVEF in approximately one-third of patients, with a decline of more than 10% observed in 11% of cases.

According to the 2022 European Society of Cardiology (ESC) cardio-oncology guidelines, baseline cardiovascular risk assessment should be performed prior to initiation of TKI therapy. This evaluation includes clinical examination, blood pressure measurement, and electrocardiography (ECG) for assessment of the QTc interval. In high-risk patients, particularly those previously treated with anthracyclines, baseline echocardiography is also recommended. During treatment, home blood pressure monitoring should be performed daily during the first cycle, during dose titration, and subsequently every 2–3 weeks. QTc interval monitoring is recommended during dose adjustments, when concomitant QT-prolonging medications are

used, or in the presence of electrolyte imbalances. For the management of arterial hypertension, angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs) are recommended as first-line agents, with dihydropyridine calcium channel blockers as alternative or adjunctive therapy.

Alternative Cytotoxic Chemotherapy

Trabectedin exerts its antitumor effect by interfering with DNA repair mechanisms, inhibiting transcription-coupled nucleotide excision repair, and modulating the tumor microenvironment. It is primarily used as a later-line treatment for locally advanced soft tissue sarcomas (STS), particularly in liposarcoma and leiomyosarcoma subtypes, and has demonstrated superior disease control compared with dacarbazine in a phase III clinical trial. In that study, trabectedin was associated with a higher incidence of heart failure (5.0% vs. 2.3%), cardiomyopathy (3.7% vs. 2.3%), and other cardiac failure events (2.9% vs. 0.6%).

Risk factors include age ≥ 65 years, pre-existing cardiovascular disease, reduced left ventricular ejection fraction (LVEF), and prior exposure to high-dose anthracyclines (≥ 300 mg/m²). However, in the LMS-04 trial, the combination of doxorubicin and trabectedin was not associated with increased cardiotoxicity compared with doxorubicin alone, possibly due to the use of lower doses of both agents.

Baseline assessment of LVEF and subsequent monitoring every 2–3 months are recommended during trabectedin therapy. Other cytotoxic agents commonly used in sarcoma treatment include eribulin, gemcitabine, docetaxel, and ifosfamide. Eribulin, a microtubule inhibitor, generally has a low risk of cardiotoxicity, but may cause QTc prolongation; therefore, baseline electrocardiography (ECG) and regular monitoring are recommended. Gemcitabine has been associated, based on observational data, with myocardial ischemia, pericardial disorders, and supraventricular arrhythmias. Docetaxel and ifosfamide are rarely associated with cardiovascular toxicity and are mainly used as part of combination chemotherapy regimens.

Immune Checkpoint Inhibitors (ICIs)

Results from small open-label phase II clinical trials indicate that some patients with locally advanced, unresectable, or metastatic sarcoma who have received at least one prior line of systemic therapy—particularly those with undifferentiated pleomorphic sarcoma (UPS) and related subtypes—may benefit from pembrolizumab monotherapy or the combination of ipilimumab and nivolumab. Immune checkpoint inhibitors (ICIs) may be associated with the following cardiovascular toxicities:

- Myocarditis
- Pericardial disease
- Heart failure

- Myocardial infarction
- Cerebrovascular ischemic events

Among these, myocarditis is the most serious and life-threatening complication. Although rare (approximately 1%), it is associated with high mortality (30–50%), and the risk is reported to be higher with dual ICI therapy.

Therefore, the following preventive and diagnostic approaches are recommended:

- Baseline electrocardiography (ECG) and troponin assessment prior to initiation of therapy.
- Baseline echocardiography in high-risk patients.
- Immediate discontinuation of ICI therapy and initiation of high-dose glucocorticosteroids if myocarditis is suspected.

The safety of reinitiating therapy after an episode of ICI-associated cardiotoxicity remains unclear and requires individualized risk–benefit assessment.

Survivorship: Life After Soft Tissue Sarcoma

Advances in screening, diagnostic, and treatment methods have led to improved survival rates among sarcoma patients, who are expected to constitute a significant proportion of cancer survivors—a population projected to exceed 20 million in the United States by 2030.

The overall 5-year survival rate for soft tissue sarcomas (STS) ranges from approximately 60% to 80%, although this varies significantly depending on histological subtype, tumor resectability, and stage of disease.

Cancer survivors are at risk of developing long-term and late treatment-related complications. In particular, delayed anthracycline-associated cardiotoxicity remains a major cause of morbidity and mortality in this population.

Epidemiological data indicate that individuals treated with anthracyclines during childhood and surviving into adulthood have a higher incidence of heart failure compared with control groups. Therefore, long-term follow-up, management of modifiable risk factors, and early detection and treatment of clinical manifestations are of critical importance.

From the time of initial sarcoma diagnosis through survivorship, the implementation of a multidisciplinary approach—including cardio-oncologists—is essential to minimize cardiotoxicity and preserve long-term cardiovascular health.

The International Cardio-Oncology Society (IC-OS) and the Heart Failure Association of the European Society of Cardiology have developed recommendations for stratifying patients into low-, moderate-, and high-risk groups for cardiotoxicity and for applying appropriate monitoring strategies; these approaches have subsequently been incorporated into ESC cardio-oncology guidelines.

Referral of sarcoma patients with prior anthracycline exposure to specialized survivorship clinics that include cardio-oncological evaluation is advisable.

In patients belonging to moderate- and high-risk groups, strict control of blood pressure, lipid profile, and glucose metabolism is of particular importance.

The optimal strategy for long-term echocardiographic monitoring remains a matter of debate. According to ESC guidelines, echocardiography is recommended every 2–5 years in patients at least at moderate risk. However, the overall duration, clinical effectiveness, and cost-effectiveness of such monitoring have not yet been fully established.

Conclusion

Although advances in scientific research have deepened our understanding of the biology and clinical features of soft tissue sarcomas (STS), this heterogeneous group of tumors remains challenging in terms of diagnosis and treatment.

Available retrospective data suggest that a multimodal treatment approach is associated with more favorable clinical outcomes in this patient population.

Due to the widespread use of high cumulative doses of anthracyclines in STS treatment, cardiotoxicity must be carefully considered both during active therapy and throughout long-term survivorship.

While other cytotoxic agents generally have a more limited impact on cardiac function, tyrosine kinase inhibitors and immune checkpoint inhibitors are characterized by distinct and clinically significant cardiovascular toxicity profiles.

In particular, systematic monitoring and timely intervention are essential for the early detection of TKI-associated arterial hypertension and ICI-related myocarditis.

In clinical practice, a more cautious approach and implementation of long-term follow-up strategies are especially warranted in pediatric patients and in individuals with increased cardiovascular risk due to comorbid conditions.

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