

# **CURRENT APPLICATIONS OF CHEMOTHERAPY IN TREATMENT OF CARDIAC CANCERS**

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## **Abstract**

Malignant cardiac tumors invite challenges to the efficacy of their treatment. Outside of their benign counterparts, malignant primary cardiac tumors - particularly sarcomas - necessitate approaches that involve a combination of treatments. One of those treatments, chemotherapy, is effective as both an adjuvant and palliative treatment, and its administration in tandem with either radiotherapy or surgical resection has contributed to greater rates of post-treatment survival. Most notably, reductions in tumor size prior to resection have been demonstrated by neoadjuvant chemotherapy in order to improve surgical outcomes. Showing promise in further increases of survival rates advances in chemotherapeutics such as anthracyclines and ifosfamide have established greater efficacy in clinical trials. However, factors like cardiotoxicity from the utilization of chemotherapy and the anatomical barriers of the heart hinder the effectiveness of the application of these new therapeutics. Outside of these limitations, the nature of late-stage diagnosis and patient age play a role in limiting the efficacy of chemotherapy. To limit the side effects of pharmaceuticals, there is a need for cardioprotective strategies and the development of targeted therapies; personalized and multimodal approaches to improve patient outcomes would be optimal as well. As more pharmaceuticals in chemotherapy are developed, future research into the chronic effects of the administration of the pharmaceuticals and alternative therapeutic avenues should be enacted.

## Introduction

A significant majority of cardiac tumors are primarily benign, yet malignant primary cardiac tumors are still present within populations (Bussani et al.). However, both of these incidence rates are inconsequential to the rate of secondary cardiac tumors. Benign cardiac tumors are largely characterized as myxomas and are typically diagnosed in adults in the latter half of their expected lifespan. Malignant primary cardiac tumors, on the other hand, are predominantly sarcomas.

Currently, the treatment options for cardiac tumors vary significantly as the therapies utilized are dependent on the tumor's characteristics - specifically its type, location, and classification as either benign or malignant. For most benign cardiac tumors, surgical resection is the most prevalent treatment due to its minimal risk for embolic events where a blood vessel can experience blockage (Bussani et al.). Most malignant tumors will have treatments that encompass a combination of surgery, chemotherapy, and radiotherapy, yet what strengthens tools such as chemotherapy and radiotherapy is their ability to also be utilized for adjuvant therapies to ensure there is no return of cancer (Barreiro et al.). Chemotherapy and radiotherapy may be also utilized as options for palliative care - especially for unresectable tumors - to mediate symptoms (Joshi et al.). Therefore, a multidisciplinary approach is required to treat both benign and malignant tumors with tools like chemotherapy and radiation offering versatile uses to best aid the healthcare process.

Chemotherapy is specifically a promising treatment with the development of new pharmaceuticals to not only treat malignant tumors but also increase the efficacy of the treatment overall. This potential is due to the increase in more advanced pharmaceuticals. Notably, the development of anthracyclines - a variant of antibiotics - and ifosfamide have increased the survival rates of malignant cardiac tumor treatment (Farzin and Nejad; Bussani). Neoadjuvant chemotherapy applied prior to resection has taken advantage of these advanced pharmaceuticals as it has seen an increase in survival for patients with minimal to no progression of cancer (Siontis et al.; Tyebally et al.).

While the improvements in chemotherapy show significant promise, there are still challenges that surround the usage of chemotherapy due to the anatomical and physiological characteristics of the heart and the nature of the treatment. The entrance of the chemotherapeutic agents into the cardiac tissue can be difficult (Siontis et al.). If the chemotherapeutic agents are not able to enter their target areas, then the treatment will be ineffective. Moreover, due to the nature of the malignant cardiac tumor, the aggressiveness of the tumor often leads to late-stage diagnosis, where treatment overall - including chemotherapy - is hindered in its efficacy rates (Tyebally et al.; Siontis et al.). There is also the risk of side effects caused by reactions to specific variations of anthracyclines that can cause cardiotoxic symptoms that can worsen heart conditions and lead to further complications, even heart failure. This is poignant for patients with preexisting

compromised heart function (Ng et al.). Therefore, the usage of chemotherapy - while showing promise - can be ineffective or adverse due to the nature of using pharmaceuticals as well as the timing of its application.

## **Methodology**

The literature review utilized a systematic approach to identify appropriate literature. The database search included PubMed, Google Scholar, and the Cochrane Library; institutional access was utilized for journals that were not open access. Keywords included but were not limited to: "cardiac tumors," "neoadjuvant care," "malignant tumor imaging," "treatment efficacy," "cardiotoxicity," "doxorubicin," and "gemcitabine." In addition, the Snowball method was a tool that was used to identify approximately 25% of the literature referenced in this review.

The criteria used to obtain the literature discussed in the review required papers written within 10 years of the publication of this review in order to ensure the most accurate information was analyzed. A few exceptions to this mandate were papers that sought a historical perspective on the treatments discussed. The studies selected specifically focused on cardiac tumors and their treatments, particularly chemotherapy and the developments in chemotherapeutic agents; this included clinical trials, retrospective studies, case reports, and reviews.

The selection process involved an initial screening of titles and abstracts using keywords stated previously. Further reading of the full text by the researcher was then employed to confirm the validity of including the publication in the literature review. Data extraction included the classification of studies based on common themes previously established, including the specific chemotherapeutic agents used, efficacy, side effects, and patient outcomes. The data was presented using a qualitative approach, and quantitative data was presented via tables or statistics to sustain the findings whenever necessary.

## **Overview of Cardiac Tumors**

First, it is important to understand the types of cardiac tumors in order to delve into how chemotherapy is currently being utilized in healthcare. The classification of benign cardiac tumors can be further distinguished based on their location, structure, and resulting symptoms. Myxomas are the most prevalent variety; they are typically located in the left atrium and have a gelatinous consistency. Myxomas can be dangerous as patients with myxomas can be prone to embolic events (Bussani et al.). Rhabdomyomas are another type of benign cardiac tumor that is associated with pediatrics and children with tuberous sclerosis. It can be found in any cardiac chamber (Karigyo et al.). Another class of tumors that are abundant in children is fibromas, which are found in the ventricles. Fibromas cause obstruction and are associated with arrhythmias (Bussani et al.). There are also lipomas - which consist of mature adipose tissue - and are asymptomatic. Lipomas can be located in multiple parts of the heart, including the endocardium and pericardium. Less frequent tumor classifications also include hemangiomas -

vascular tumors that can also be found in the heart - and papillary fibroelastomas which can be found in heart valves and can be responsible for embolic complications (Karigyo et al.). Despite the variation in composition and location, chemotherapy can be utilized as an effective treatment for benign cardiac tumors (Siontis et al.; Tyebally et al.).

Malignant cardiac tumors are defined by their ability to have their cells divide without restriction. Malignant cardiac tumors are primarily classified as primary sarcomas, are much rarer, and include angiosarcomas, rhabdomyosarcomas, and undifferentiated pleomorphic sarcomas. Tumors that are malignant are characterized by aggressive behavior, a high rate of metastasis to other regions of the patient's body, and a median survival between 6 and 11 months (Hendriksen et al.). Chemotherapy can be effective with this type of tumor as it can slow the progression of the tumor, yet it is important to note that it is not a cure as this condition has a poor prognosis with all current treatments.

Diagnosing cardiac tumors relies on imaging techniques as these techniques help inform users what exactly should be treated. Transthoracic echocardiography (TTE) is a prioritized imaging technique that can give detailed evaluation - particularly on the left side of the heart and can distinguish between tumors and thrombi (Karigyo et al.; Bussani et al.). Similarly, cardiac computed tomography (CT) can also differentiate between tumors and thrombi. Where CT excels is a high spatial resolution that can characterize tissues and identify metastases (Karigyo et al.; Gatti et al.). Moreover, cardiac magnetic resonance imaging (CMR) is another imaging technique that provides tissue characterization and multiplanar assessment of cardiac structure. This makes it the most comprehensive imaging modality (Gatti et al.; Lopez-Mattei et al.). Lastly, biopsy offers the ability to hold histopathological evaluation of the tumor. While being the highest tier for definitive diagnosis, biopsies are reserved for when results are inconclusive (Gatti et al.; Bussani et al.).

Surgical resection is a medical intervention that is considered standard for the treatment of localized tumors. This is especially poignant for malignant cardiac tumors such as sarcomas and angiosarcomas. Complete wide surgical resection is important as it has suggested higher survival rates, despite the aggressive nature of some malignant cardiac tumors. Even in circumstances where total resection is not feasible, palliative surgery can still be performed in order to alleviate symptoms caused by a mass or obstruction (Hendriksen et al.).

For specific classes of tumors like cardiac myxomas, surgical excision is relatively simplistic. The procedures can be done via median sternotomy - a surgical procedure where a vertical incision is made through the breastbone and chest area to access the heart - or other minimally invasive techniques, depending on the location of the tumor. However, complicated tumors such as high-grade angiosarcomas require other tools to be necessary - including chemotherapy - to increase the survival outcome of the patient.

## **Chemotherapy in Cardiac Tumors: Background**

Initially, pharmaceutical agents and treatments used in chemotherapy for primary malignant cardiac tumors (PMCTs) were limited and based on older agents. Anthracyclines like doxorubicin were then introduced; an issue that soon arose was the cardiotoxic side effects, including a decrease in ejection from the left ventricular area from approximately 10% to 53% (Linders et al.). Recently, there has been a shift in comprehension in the healthcare community where chemotherapy is no longer a standalone treatment, but an adjunct tool to be applied before or after a surgical procedure (Appiah et al.).

Administration of chemotherapy has improved as well, which has led to an increase in efficacy for patient outcomes and a reduction in side effects. Lipid-based carriers have been employed to encapsulate chemotherapeutic drugs in order to enhance drug absorption rates and the accurate targeting of tumor cells (Wendler). Near the end of the 20th century, serotonin antagonists such as ondansetron, also known as Zofran, have been employed to better patient experience while in palliative treatment. Recently, with the rise of the use of personalized medicine, chemotherapy is being utilized more effectively in order to treat cardiac tumors (Wall et al.).

## **Common Chemotherapy Agents Used for Cardiac Tumors**

Doxorubicin is an anthracycline antibiotic that has the primary function of disrupting replication and transcription in cancer cells, which eventually leads to apoptosis. Doxorubicin intercalates DNA - thereby inhibiting topoisomerase II - to prevent DNA replication and lead to apoptosis (N. Prathumsap et al.). Patients who have been administered DOX have experienced side effects including cardiotoxicity, myelosuppression, nausea, vomiting, and alopecia. However, the integration of cardioprotective agents like dexrazoxane into the patient's treatment can mitigate the risk of cardiotoxicity (S. Upadhyay et al.); supportive care measures such as antiemetics and growth factors can also be added to minimize side effects associated with DOX. Therefore, while DOX has shown promise in combating malignant cardiac tumors, further research must be done in order to reduce side effects for the patient when specifically administered in cardiac tumor treatments.

Another commonly used chemotherapeutic agent is paclitaxel. This drug is an antimicrotubule agent that has been shown to be particularly effective against angiosarcomas. It serves to prevent depolymerization of the microtubules, which disrupts mitosis and leads to cell cycle arrest and apoptosis. Compared to doxorubicin, paclitaxel demonstrates fewer adverse risks for its patients, yet users can still have side effects that myelosuppression, peripheral neuropathy, hypersensitivity reactions, and gastrointestinal disturbances (Chmielewski-Stivers et al.).

Ifosfamide is a pharmaceutical used in chemotherapy that targets a different mechanism of cancerous cells, and it is an alkylating agent. Ifosfamide functions by promoting the formation of DNA cross-links as well as preventing DNA synthesis and thus function, which eventually

correlates to cell death. Ifosfamide has shown promise in being used in chemotherapeutic treatment in conjunction with other agents as it displays an ability to target cancer cells with particularly high division rates. In one case report - involving high-grade cardiac leiomyosarcoma, ifosfamide was integrated as part of a treatment regimen: the patient was able to achieve progression-free survival (PFS) for two years after the treatment (Janopaul-Naylor et al.). Like ifosfamide, Gemcitabine is an agent that inhibits the synthesis of DNA. It is a nucleoside analog that has shown potential in treating malignant cardiac tumors. Common side effects include myelosuppression, gastrointestinal disturbances, flu-like symptoms, rash, and liver enzyme elevations.

### **Efficacy of Chemotherapy in Treating Cardiac Tumors**

Chemotherapy has shown to be a more serviceable tool. A study that utilized data from the Surveillance, Epidemiology, and End Results (SEER) Program showed that patients with PMCTs who received chemotherapy had a median overall survival of 18 months. This is significantly greater than the 3 months of post-treatment survival for patients who did not receive chemotherapy (Appiah et al.). That same study found that patients who received chemotherapy had a 44% reduced risk for all-cause mortality and a 37% reduced risk for cancer-related mortality. In terms of the impact on the well-being of the patient's heart, a 73% reduced risk for cardiovascular disease (CVD) mortality was obtained (Appiah et al.). Furthermore, neoadjuvant chemotherapy for individuals with right heart sarcomas was administered prior to surgical resection resulting in a median survival of 20 months for patients, compared to 9.5 months without chemotherapy. Specifically for complete surgical resection (R0) resection, patients were able to achieve a median survival of 53.5 months for R0 status (Abu Saleh et al.). Neoadjuvant chemotherapy enhances the outcomes of surgery by reducing the size of the tumor and improving the ability for the tumor to be resectable. Without this addition to medical interventions, survival rates decrease to approximately 10% at 12 months (Abu Saleh et al.). Therefore, clinical trials and respective studies have shown that chemotherapy has improved survival rates in patients, so the involvement of chemotherapy in the treatment of cardiac tumors is shown to be more beneficial.

However, the efficacy of chemotherapy can be enhanced by the integration of other tools as well. Radiotherapy is one such method as it is a treatment method that utilizes radioactive substances or rays of short wavelength and high energy to damage and stop the growth and division of tumor cells. For patients with PMCTs, approaches that combine both methods have had higher rates of efficacy. One study found that patients with Stage 3 PMCTs - meaning the tumor has become significant enough to propagate to nearby tissues or lymph nodes - went on to have 15 months of post-treatment survival following treatment that had combinations of chemotherapy and radiation therapy. Patients not given this treatment only had 3 months of post-treatment survival. (Appiah et al.).

Another factor that impacts the efficacy of chemotherapy is the type and stage of a tumor for a patient. Angiosarcomas specifically respond relatively favorably - albeit still poor - to systemic cytotoxic chemotherapy compared to other cancerous tumors. One study found that the median survival for primary cardiac sarcomas in patients who received chemotherapy was reported to be 18 months. In contrast to this, patients with non-angiosarcoma subtypes - which include fibrosarcomas and leiomyosarcomas - have lower survival rates that result in approximately 3 to 6 months without effective treatment (Appiah et al.).

Patient demographics - especially age - are also an influence on the effectiveness of chemotherapy. Older patients have a higher risk of having other comorbidities. These comorbidities serve as complications to treatment regimens, which necessitates adjustments to the dosing involved in chemotherapy. Compared to younger individuals, older patients have poorer organ function and hematopoietic potential, which again minimizes the efficacy of chemotherapy. Thus, chemotherapy can be limited by factors that consider the age of the patient: this must be considered when assessing whether chemotherapy should be administered in the patient's treatment.

### **Case Studies and Clinical Trials**

Studies of the efficacy of chemotherapy highlight its significance for managing cardiac tumors. In one case report, patients who had diffuse large B-cell lymphoma (DLBCL) were diagnosed with percutaneous ultrasound-guided core needle biopsy (PUS-CNB). The patients displayed a positive response to the chemotherapy - some patients experienced a complete disappearance of cardiac lesions (Xie et al.). In terms of the pharmaceuticals applied in the chemotherapeutic treatment, new doxorubicin-based regimens have shown to be effective in reducing the size of cardiac tumors and improving overall survival outcomes in primary cardiac sarcomas, which is the most common malignant tumor that healthcare officials will treat - although malignant cardiac tumors are rarer in comparison to other variations of malignant tumors in general oncology (Gatti et al.). Moreover, a combination of the application of chemotherapy with surgical resection has increased the post-treatment survival for cardiac angiosarcomas to approximately 32 months in the patient group. Therefore, the use of these new advancements in chemotherapy has shown to be effective in the treatment of patients (Karigyo et al.; Gatti et al.).

Major clinical trials focusing on chemotherapy for cardiac tumors have primarily targeted specific malignancies, such as cardiac sarcomas and lymphomas (Kumari et al.; Patel et al.). A trial assessed chemotherapy's efficacy in primary cardiac lymphoma, highlighting the use of monoclonal antibodies like rituximab (Joshi et al.). These trials underscore the importance of multimodal treatment approaches to enhance survival rates and manage symptoms effectively (Hendriksen et al.).

Pharmaceuticals outside of doxorubicin have been explored as well in order to mitigate some of the cardiotoxic effects that doxorubicin holds. One study utilized monoclonal antibodies like

rituximab to treat primary cardiac lymphomas, which saw improved overall survival, although the increase was not statistically significant in all cases (Karigyo et al.). Moreover, ongoing trials have explored the efficacy of the application of chemotherapeutic agents such as ifosfamide with targeted therapies like pazopanib in cardiac angiosarcoma, yet these trials are still in their infancy (Karigyo et al.; Patel et al.).

## **Discussion**

The literature on chemotherapy for cardiac tumors reveals key insights regarding treatment efficacy, survival outcomes, and challenges associated with these rare malignancies. PMCTs are associated with poor prognosis and limited treatment options, making chemotherapy a significant area of interest. Studies indicate that patients receiving chemotherapy, particularly in conjunction with surgical resection, demonstrate improved survival rates (Sultan et al.). The effectiveness of chemotherapy varies by tumor type, with primary sarcomas showing a 5-year survival rate of 11.5% (Sultan et al.). Cardioprotective strategies and the administration of targeted therapies and immunotherapies are critical for minimizing cardiotoxicity and enhancing treatment efficacy, albeit the research is still relatively in its early stages (Liang et al.; Wall et al.).

The literature highlights the efficacy of clinical applications of chemotherapy for cardiac tumors. PMCTs correlate with poor prognosis and limited treatment options: this as a result frames chemotherapy as a strong area of interest. There has been an increase in total literature for chemotherapy as health officials continue to explore new avenues and pharmaceuticals to utilize. Studies indicate that patients receiving chemotherapy, particularly in conjunction with surgical resection, demonstrate improved survival rates. However, it is important to note that the efficacy of chemotherapeutic treatments is influenced by the class of the tumor being treated (Sultan et al.). In addition, many of these drugs have side effects in their application, including cardiotoxicity. Therefore, cardioprotective strategies - including targeted therapies and immunotherapies - must be and are being developed to minimize cardiotoxicity and increase treatment efficacy. Cardioprotective agents - such as dexrazoxane - have displayed promise in mitigating cardiotoxicity (Liang et al.). Immunotherapies and other targeted therapies are more recent explorations that offer to reduce collateral damage to cardiac tumors while maintaining effectiveness against tumors (Wall et al.). However, the concern for minimizing the exacerbation of side effects still remains prevalent with these new therapies.

That being said, there are research gaps that must be addressed. While many studies do suggest that the application of adjuvant chemotherapy has a positive influence on the post-treatment survival of the patient, other conflicting research offers an alternative hypothesis that chemotherapy has little influence on the treatment of cardiac tumors (Liang et al.). Thus, this uncertainty must be addressed as the role of chemotherapy is still undefined although it is worth noting that chemotherapy is integral in current treatments for some cardiac tumors. As stated previously, the effectiveness of chemotherapy also varies by the class of the tumor of the patient.



This variance can make it difficult to establish a uniform treatment for all the histological varieties of cardiac tumors (Llombart-Cussac et al.). This offers the use of personalized treatment for each individual patient. Research into the molecular and cellular mechanisms of each class can offer new insights to treat each specific variant of cardiac tumor.

Furthermore, the chronic implications of chemotherapy is a topic that has not been explored as thoroughly, which must be addressed in order to assess the long-term effects of pharmaceuticals like anthracyclines or other potentially cardiotoxic agents (Liang et al.). A longitudinal study to address these effects is necessary as the number of individuals with underlying heart conditions is increasing: this means more patients will be vulnerable to cardiotoxic agents administered through chemotherapy. The interplay between cardiovascular health and cancer risk, including reverse cardio-oncology, warrants further exploration (Liang et al.). Larger multimodal studies must be established in order to address these interdisciplinary research gaps by providing robust data on the efficacy of adjuvant chemotherapy.

## **Conclusion**

The literature review for chemotherapeutic treatment for cardiac tumors illustrates that the utilization of chemotherapy - particularly in tandem with surgical resection - has been shown to significantly improve post-treatment survival. Studies support this notion with reduced cancer-related and all-cause mortality with chemotherapy, specifically with cardiac tumors. However, tailored treatment for each individual patient is based on other underlying conditions they may have or tumor heterogeneity as some classes of tumors are more effectively reduced with chemotherapy than others, specifically sarcomas. With the poor prognosis of PMCTs, understanding the efficacy of chemotherapy as a whole as well as the effectiveness of different types of agents is crucial. The potential for cardiotoxicity provides a necessary avenue to assess the balance between effective cancer treatment and cardiovascular health, which underscores the importance of cardio-oncology.

Future research will be set on determining the chronic effects of chemotherapeutic agents as well as exploring new subsets as well. This will improve the management and post-treatment survival of the patients as the healthcare field as a whole shifts to personalized care and integrating multimodal treatment.

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