REVIEW ARTICLE

Cardiovascular Issues in Patients with Malignant Lymphoma: A Narrative Review

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Conflict of interest
The authors have no conflicts of interest to declare.

Search; selection criteria
The author searched PubMed for articles published in peer-reviewed recent English literature during the period 1993–2022. The search terms "malignant lymphoma," "cardiac lymphoma," and "cardiovascular" and the name of the word of interest as search terms. Although the author tried to cite seminal studies when necessary, representative articles were often selected. In addition to that, Williams Hematology 9th edition was also referred to.

ABSTRACT
Cardiovascular issues are important concerns in malignant lymphoma treatment. These issues can be broadly categorized into two groups: the invasion of malignant lymphoma into the heart and cardiovascular disease related to malignant lymphoma treatment. In terms of malignant lymphoma invasion of the heart, the presence of a heart lesion of malignant lymphoma often presents with heart-related symptoms and findings such as chest pain, heart failure, and arrhythmias. Notably, heart failure and arrhythmias can be fatal. The identification of heart lesions of malignant lymphoma will result in appropriate management and survival improvement. As for cardiovascular disease associated with malignant lymphoma treatment, the incidence and types of cardiovascular disease, management, and follow-up planning should be identified before starting treatment. This identification and plan will allow an understanding of the risk of developing cardiovascular disease and appropriate management and follow-up. In clinical practice, it is important to keep in mind that cardiac issues in patients with malignant lymphoma should be identified, assessed, and managed before initiating treatment.

Introduction

Malignant lymphoma (ML) is a heterogeneous disease. MLs usually originate in lymph nodes or tissue in other sites, also known as extranodal lesions. MLs can be localized or widespread at diagnosis. All patients with ML are required to examine the distribution of lymphadenopathies, extranodal lesions, and disturbances of affected organs. Additionally, liver and spleen size should be assessed. Patients with ML may also have B symptoms, including fever (i.e., temperatures of >38°C for three consecutive days), drenching night sweats, or weight loss of >10% within the preceding 6 months. Rapidly progressing MLs more likely to involve extranodal lesions.[1]

Malignant lymphoma can originate in the heart although the incidence is rare. It is called primary cardiac lymphoma (PCL). Additionally, MLs can involve the heart as extranodal lesions. Patients with ML heart lesions present with various symptoms and findings, such as heart failure (HF), arrhythmia, and tamponade, and can be fatal.[2,3] Treatment can prolong survival.[4]

Patients with ML have a growing cardiovascular disease (CVD) epidemic because therapy development and improved survival have resulted in increased CVD. Identifying the increased risk of CVD and assessing CV risk are required. Appropriate assessment may result in reducing CVD. A personalized approach to CV risk would allow patients with ML to complete their treatments free from CVD and improve survival.[5]

Cardiovascular issues are important concerns in ML treatment.[2,6] The issues can be divided into two categories, an invasion of ML into the heart and CVD associated with ML treatment. In this narrative review, we aim to provide perspective on cardiovascular issues in patients with ML, particularly from two perspectives: invasion of ML into the heart and CVD related to ML treatment. We will provide an overview of each issue, identification of its risk factor and development, and outline the appropriate practices for assessment, follow-up, and management.

Malignant lymphoma involving the heart
Epidemiology

The report of 12,485 autopsies (1972–1991) at Queen Mary Hospital in Hong Kong, reported 0.056% (7 cases) and 1.23% (154 cases) incidences of primary and secondary heart tumors, respectively. The seven cases of primary cardiac tumors consisted of two myxomas, two rhabdomyomas, two hemangiomas, and one lipoma. Thus, this report did not include ML in primary cardiac tumors. Therefore, the incidence of PCL is rare. Malignant neoplasms invading the heart include the lung tumor (31.7%), esophagus tumor (28.7%), and ML (11.9%), in order of frequency.[7,8] Thus, PCL is very rare, but ML is one of the common malignant neoplasms invading the heart. Figure 1 shows schematic of cardiac tumors.

Secondary cardiac tomor — The frequency of autopsies was 1.23%

>>> Primary cardiac tumor — The frequency of autopsies was 0.056%

Malignant neoplasms invading the heart in order of frequency
① Lung tumor (31.7%)
② Esophagus tumor (28.7%)
③ Malignant lymphoma (11.9%)

Accounted for 75%

Accounted for 15%

Benign
① Myxoma
② Lipoma
③ Papillary fibroblastoma

Malignant
① Sarcoma
② Primary cardiac lymphoma
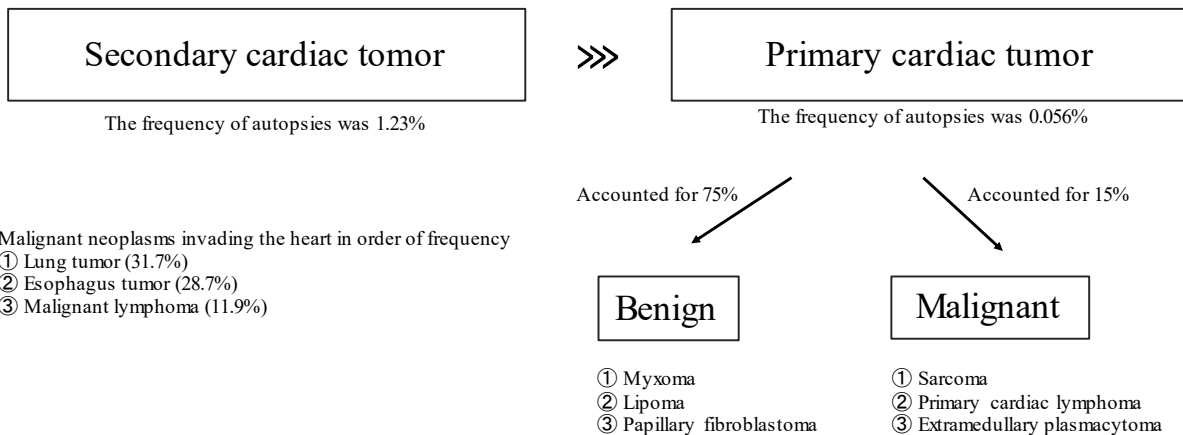③ Extramedullary plasmacytoma

Figure 1: Schematic of cardiac tumors - Reference (7),(8)

Symptoms and findings

A retrospective study reported the symptoms and findings of patients with PCL.[2,3] The symptoms included chronic chest pain (46%), dyspnea (54%), and cough (8%). The findings included congestive heart failure (CHF) (78%), tamponade (8%), arrhythmia (23%), B symptoms (23%), superior vena cava syndrome (15%), and asthenia (15%).[2] Additionally, among arrhythmias accompanied by PCL, complete atrioventricular block is a major presentation.[9] Furthermore, another study reported fatal events among patients with PCL. Among patients with PCL with arrhythmias, 11% had fatal arrhythmias, 2% presented with sudden cardiac death, and 6% presented with embolic phenomena attributed to PCL, including 3% with pulmonary embolism and 2% with cerebrovascular accident. Pulmonary embolism was fatal in 2% of patients, and cerebrovascular accidents in 0.5% of patients. Tamponade physiology was noted in 18.2% of patients but was fatal in only 0.5%.[3] Thus, patients with PCL often present with chronic chest pain and dyspnea. Most patients develop heart failure.

Imaging tests
The imaging features of a cardiac lesion in ML are described below.

Echocardiography, computed tomography (CT), and magnetic resonance imaging (MRI) are useful for diagnosis and subsequent treatment efficacy evaluation of ML invading the heart. Echocardiography is the simplest examination. CT assesses the extent of the tumor. MRI is used for early detection and treatment efficacy determination.[4]

Echocardiography usually shows ML lesions as hypoechoic masses. Pericardial effusion and thickening are often observed. Contrast echocardiography, which is microbubbles administered transvenously to produce intracardiac contrast, myocardial staining, and Doppler signal enhancement, shows an enhanced shadow compared to the surrounding myocardium. CT can assess the extent of the tumor. CT shows a low to iso absorptive mass shadow with little calcification compared to the adjacent myocardium and skeletal muscle. The delayed layer of contrast-enhanced CT often shows a less distinct heterogeneous enhancement, and lymphadenopathy may also be observed. The valve has little infiltration, but it spreads along the epicardial surface and envelops the coronary artery as well as the aortic root. Additionally, pericardial thickening and effusion are observed. MRI is used for early detection and treatment

efficacy determination. It can accurately evaluate tumor mobility, the site of attachment, and nearby cardiac structures. T1-weighted images show low to equal signals, and T2-weighted images show equal to strong signals compared to normal myocardium. The mass is enhanced on stress-perfusion MRI, and a thrombus appears in the low-signal range. This method evaluates myocardial blood flow distribution based on the dynamics of gadolinium contrast agents on myocardial distribution in a dilated myocardium with a vasodilator. Delayed contrast-enhanced MRI shows no central enhancing shadows and heterogeneous contrast uptake.[4]

Anatomical features

Of PCLs, 77% were located in the right atrium. An invasion of the right ventricle and/or the interatrial septum was observed in 16% and 21% of PCLs, respectively. Conversely, left heart invasion was observed in 31% of cases. Endoluminal growth was identified in 38% of patients. The size of the ML lesion in the heart ranged from 20 to 110 mm in maximal diameter (median: 47 mm). [2] Thus, PCL is often located in the right atrium and is accompanied by pericardial effusion.

Pathology

Pathological subtypes of PCLs were diffuse large B cell lymphoma in 92% of cases and Burkitt lymphoma in 8%.[2] Thus, the majority of pathological subtypes of PCLs are diffuse large B cell lymphoma.

Clinical course and prognosis

The median overall survival of patients with PCL was 63 months. However, the range of survival time is long, from 4.7 to 121.3 months.[2] Thus, survival greatly varies from case to case. The recurrence after first-line chemotherapy was observed in 55% of cases.[2] Another study revealed that the cause of death was HF at 40%. This was followed by sepsis or severe infection (26%) and ML progression (23%).[3] Thus, HF is the most frequent cause of death among patients with PCL.

Take home message

· PCL is rare. Conversely, ML is one of the common malignant neoplasms that metastasize to the heart.

· Patients with ML with heart lesions present various symptoms and findings, such as heart failure, arrhythmia, and tamponade, which can be fatal.

· Echocardiography is the simplest examination and often reveals hypoechoic masses in the right atrium and peripheral effusions as ML lesions.

· PCL often occurs in the right atrium and is often associated with pericardial effusion.

· The majority of pathological subtypes of PCLs are diffuse large B cell lymphoma.

· Prognosis of patients with PCL varies widely from case to case.

Cardiovascular disease associated with malignant lymphoma treatment

Incidence of CVD associated with malignant lymphoma treatment

According to a cohort study of 3063 patients newly diagnosed with ML without CVD history, the cumulative incidence of CVD among ML patients treated with chemotherapies and/or radiotherapy at 10 years was 10.7% (95% confidence interval [CI]: 9.5%–12.1%). However, participants in this study had the following characteristics. The median age of the patients with ML was 59 years (range: 18–95). Upon ML diagnosis, 68.4% of patients were overweight or had obesity, 39.5% had smoked ever, 32.0% had hypertension, and 37.5% had hyperlipidemia. Regarding the initial therapy, 51.3% of patients were treated with therapy, including anthracycline. Multivariable analysis revealed the following as the risk factors associated with CVD among ML patients treated with chemotherapies and/or radiotherapy: increasing age (hazard ratio [HR] = 1.05 per year), male sex (HR = 1.36), current smoker (HR = 2.10), body mass index of > 30 kg/m^2 (HR = 1.45), and anthracycline use (HR = 1.57).[10] Other risk factors associated with CVD among ML patients treated with chemotherapies and/or radiotherapy include: previous CVD such as heart failure, cardiomyopathy, valvular heart disease, myocardial infarction, coronary artery disease, and angina; cardiac biomarkers such as elevated baseline troponin and brain natriuretic peptide (BNP) and NT-proBNP; lifestyle risk factors such as current smoking, smoking history, and obesity. Therefore, identifying these risk factors of CVD before ML treatment may predict the onset of CVD and provide an opportunity to modify these risk factors.

Importance of cardiovascular risk factors assessment before starting treatment

Increased CVD risk identification and assessment are required before starting CV toxic chemotherapy. Hence, appropriate assessment can reduce CVD. The CVD risk factor assessment and management would allow patients with ML to complete their treatments free from CVD and improve survival. Therefore, medical history of cardiac disease, a history of chemotherapy, and medical and lifestyle CV risk should be identified.[5] CVD with chemotherapy (ML treatment) can be divided into nine main categories, including myocardial dysfunction and heart failure, coronary artery disease, valvular disease, arrhythmias, arterial hypertension, thromboembolic disease, peripheral vascular disease and stroke, pulmonary hypertension, and pericardial complications.[6] The therapeutic agents associated with CV toxicity include anthracyclines, Bruton tyrosine kinase inhibitors, immune checkpoint inhibitors, chimeric antigen receptor (CAR-T) therapy, and radiotherapy.[6]

Anthracyclines

Anthracyclines include doxorubicin, daunorubicin, epirubicin, and idarubicin. Therapies, including anthracycline, are a cornerstone in the treatment of ML, sarcoma, breast cancer, and leukemia. However, anthracyclines have cardiac toxicities.[11,12] Anthracyclines develop their toxicities by producing cytotoxic reactive oxygen species through several mechanisms, including DNA topoisomerase inhibition, DNA damage response activation, and mitochondrial biogenesis and mitochondrial iron metabolism disruption.[13] The above-mentioned cohort study revealed an association between anthracyclines and an increased risk of CHF (HR = 2.71, p < 0.001) and arrhythmia (HR = 1.61, p < 0.01). However, anthracyclines were not associated with an increased risk of valvular heart disease (HR = 0.84, p = 0.58) or acute coronary syndrome (HR = 1.32, p = 0.24).[10] Thus, the cardiotoxicities of anthracycline are mainly CHF and arrhythmias.

The cardiotoxic effects of anthracycline are initially manifested as myocardial damage and, then progress to an asymptomatic left ventricular ejection fraction reduction. Ultimately, symptomatic heart failure develops.[12] The onset of cardiotoxicity of anthracycline is divided roughly into early-onset and late-onset. Early-onset cardiotoxicity usually occurs within the first few days of anthracycline administration and manifests with electrocardiogram changes (20–30%) and arrhythmias (3%). Late-onset cardiotoxicity develops up to several decades after treatment and manifests as cardiomyopathy.[12] Additionally, the incidence of CHF secondary to anthracycline is dose-dependent. Namely, the higher the total dose of anthracycline, the higher the incidence of

CHF. The frequency of CHF was 5% when the total dose of doxorubicin reached 400 mg/m², and the frequency was up to 48% when the total dose reached 700 mg/m².[6]

A previous study revealed the incidence of subclinical cardiomyopathy and defined subclinical cardiomyopathy by the decrease of left ventricular fractional shortening (<25%) without clinical signs of CHF.

Only 0.7% of patients developed CHF during the 5-year follow-up among 141 patients with the median cumulative dose of doxorubicin at 300 mg/m². Conversely, subclinical cardiomyopathy was found in 27.6% of patients. Furthermore, none of these patients had electrocardiography changes compatible with doxorubicin-induced cardiomyopathy (flattening of the T wave, prolongation of the QT interval, and loss of voltage of the R wave).[14] Thus, asymptomatic cardiomyopathy is often observed without electrocardiography changes in patients treated with an anthracycline.

However, not missing the period of asymptomatic cardiac dysfunction is essential concerning the follow-up of cardiac function after chemotherapies, including anthracyclines.

Importantly, early cardiac impairment detection will result in prompt initiation of HF treatment. Treatment with enalapril and, when possible, carvedilol was initiated after detecting left ventricular ejection fraction impairment among 201 patients with impaired left ventricular ejection fraction ≤45% due to anthracycline.

This study considered patients as responders when their left ventricular ejection fraction increased up to the normal limit by 50%, partial responders when their left ventricular ejection fraction increased at least 10 absolute points but did not reach the limit by 50%, and nonresponders when left ventricular ejection fraction increased fewer than 10 absolute points and did not reach the limit of 50%, accounting for 42%, 13%, and 45% of patients, respectively. The percentage of responders decreased as the time between the end of chemotherapy and the start of HF treatment increased. Namely, 64%, 28%, and 7% of patients responded to treatment when treatment was initiated at 1–2, 2–4, and 4–6 months, respectively. No patients responded to treatment after more than 6 months.[15] Thus, early treatment initiation may improve cardiac impairment.

Bruton tyrosine kinase inhibitor
Bruton tyrosine kinase plays a central role in the signal transduction of the B cell antigen receptor and other cell surface receptors in normal and malignant B lymphocytes. Bruton tyrosine kinase inhibitors are a therapeutic agent, especially in patients with chronic lymphocytic leukemia and mantle cell lymphoma. Ibrutinib is one of the most widely used Bruton tyrosine kinase inhibitors.[16]

A previous retrospective study reported the incidence of atrial fibrillation (AF) in 1505 adult patients treated with ibrutinib for hematologic malignancies. The estimated cumulative incidence of AF at 6 months, 1 year, and 2 years was 5.9% (95% CI: 4.2–8.0), 7.5% (95% CI: 5.5–9.9), and 10.3% (95% CI: 8.0–13.0), respectively. Thus, the estimated cumulative incidence of AF increases as the observation period increases.

Furthermore, among patients who developed AF, patients with a history of AF developed AF earlier than those without. The median time of AF onset was 10.9 (range: 0.2–63.4) and 2.2 months (range: 0.2–35.2) among patients without and with a history of AF, respectively. Furthermore, 85.7% of patients who developed AF did not discontinue ibrutinib. More than half received common anticoagulant/antiplatelet medications in this study. Thus, the majority of patients do not discontinue ibrutinib and continue it even after developing AF.[17]

Additionally, not only AF but also ventricular arrhythmias may occur with ibrutinib administration. Among 582 patients treated with ibrutinib for hematologic malignancies over a median follow-up of 32 months (range: 0.7–73 months), 94 patients developed any symptomatic arrhythmia, including 18 patients with non-AF supraventricular tachycardia. The median time to event was 16 months (range: 0.7–57.6 months) among those with ventricular arrhythmias of at least probable ibrutinib association.

Symptomatic ventricular arrhythmias developed in 11 patients, including 7 (1 sudden cardiac death, 1 ventricular fibrillation, and 2 recurrent sustained ventricular tachycardia) with a probable association with ibrutinib. The estimated 100,000 person-year ventricular arrhythmias incidence rate was 617 over the 1,134 person-years of ibrutinib exposure.[18] Notably, AF is the most frequent CVD with ibrutinib, but ventricular arrhythmias can also occur.

Immune checkpoint inhibitor
Immune checkpoint inhibitors (ICIs) are monoclonal antibodies that target immune checkpoints such as programmed death-1, programmed death ligand-1, and cytotoxic T lymphocyte antigen-4. Immune checkpoint inhibitors produce antitumor responses by blocking these key regulators of immune

tolerance.[19] Adverse events (AEs) associated with ICIs include diarrhea and/or colitis, which is the most common (occurring in ~20% of patients), and skin rash. Other less frequent AEs (occurring in 3–20% of patients) include pruritus, hepatitis, and endocrinopathies, such as hypophysitis and thyroiditis.[20] Cardiovascular disease associated with ICIs includes myocarditis, HF, ventricular arrhythmias, atrioventricular block, atherosclerotic plaque rupture, vasculitis, and myocarditis.[5] [21] Of these, myocarditis is a potentially fatal AEs. A previous study reported myocarditis associated with ICIs. Among 35 patients with myocarditis, the median time of onset of myocarditis was 34 days after starting ICIs with an interquartile range of 21–75 days. The incidence of myocarditis was 1.14%. The presentation of the patients with myocarditis included chest pain (34%), shortness of breath (71%), orthopnea (28%), paroxysmal nocturnal dyspnea (17%), and fatigue (28%). Notably, nearly all patients with myocarditis had a troponin elevation (94%) and an abnormal electrocardiogram (89%). Additionally, the left ventricular ejection fraction was normal in 51% of these patients. Fatal AEs developed in patients with myocarditis included cardiovascular death (17%), cardiogenic shock (8%), cardiac arrest, or complete heart block (8%). Causes of death included 2 sudden deaths, 2 documented ventricular arrhythmias, and 2 progressive cardiogenic shock.[22] Thus, CVD has been reported to occur even with ICIs. In particular, myocarditis can be a fatal AEs.

Chimeric antigen receptor T cell therapy
Engineered T cells with chimeric antigen receptors (CAR-T cells) boost T-cell-mediated tumor killing. However, CAR-T cells are associated with cytokine release syndrome (CRS), leading to serious complications, including cardiac and vascular dysfunction.[23] A previous cross-sectional study reported CVD associated with CAR-T therapy (tisagenlecleucel and axicabtagene ciloleucel) from 2017 to 2019. CVD associated with CAR-T therapy was classified into arrhythmias, HF, myocardial infarction, and other CVD. Cardiovascular adverse events (CVAEs) accounted for 19.7% of all AEs. Notably, CVAEs were the second most common AEs after neurotoxicity/immune effector cell-associated neurotoxicity syndrome (54.4%). The most common CVAEs were arrhythmia (77.6%), followed by HF (14.3%) and myocardial infarction (0.5%) among patients with CVD. Additionally, the mortality rate in patients with CVD was 30.1%. In adjusted multivariate analysis, CRS (odds ratio [OR]: 2.33; 95% CI,

1.48–3.65; P < 0.001) and possible immune effector cell-associated neurotoxicity syndrome (OR: 2.3; 95% CI: 1.45–3.65; P < 0.001) were significantly associated with arrhythmias. Infectious AEs (OR: 5.77; 95% CI: 2.02–16.47; P= 0.001) were significantly associated with HF.[24] Thus, CVD should be noted as the second most common AEs and one of the frequent causes of death in CAR-T therapy.

Radiotherapy
A cohort study of 4919 Hodgkin lymphoma patients reported CVD in long-term follow-up cases of Hodgkin lymphoma after treatment. The participants included Hodgkin lymphoma patients treated before age 51 years between 1965 and 2000, with a median follow-up of 20.2 years. The Hodgkin lymphoma patients experienced a 5.1-fold higher risk of death. Up to January 2018, 44.3% of patients had died. The cause of death included Hodgkin lymphoma (32.4%), secondary malignancies (32.7%), CVD (18.0%), infectious diseases (3.2%), and respiratory diseases (1.7%). Thus, CVD is one of the most frequent causes of death in long-term follow-up cases of Hodgkin lymphoma after treatment. Additionally, radiotherapy was associated with CVD mortality. Namely, patients who received supradiaphragmatic radiotherapy had a 4.3-fold (HR = 4.36, 95% CI: 2.74–6.94) increased risk of dying from CVD. However, chemotherapy, including anthracycline was not associated with CVD mortality. In comparison to Hodgkin lymphoma patients after treatment and the general population, standardized mortality ratios of CVD were increased to 5.5 (95% CI: 5.0–6.1). In detail, myocardial infarction contributed most to excess mortality (21.0% of excess cardiovascular deaths), followed by non-ischemic diseases of the cardiovascular system and cerebrovascular disease (65.0% of excess cardiovascular deaths). Furthermore, cumulative CVD mortality increased after 10 years, with a cumulative mortality of 3.1% (95% CI: 2.6–3.6%) at 20 years and 13.2% (95% CI: 11.7–14.7%) at 40 years.[25] However, it should be noted that AEs in this cohort study are associated with the total dose of approximately 40 Gy plus a relatively large irradiation area. Currently, radiation therapy with a low total dose and a relatively small irradiated area is being used to reduce these AEs.[13] Thus, CVD associated with radiation therapy is important in long-term follow-up after treatment.

Take home message

· Anthracycline cardiotoxicity is dose-dependent.

· If anthracycline-associated cardiac dysfunction is detected early and treated with HF medications, and frequently, patients have a good functional recovery.

· AF is the most frequent CVD with ibrutinib, but ventricular arrhythmias can also occur.

· CVD, including myocarditis, has been reported to occur even with ICIs.

· CVD is the second most common AEs and one of the frequent causes of death in CAR-T therapy.

· Radiotherapy was associated with CVD mortality.

Conclusion

Cardiac issues are important in patients with ML. Cardiac issues in ML can be roughly divided into two categories as an ML invasion into the heart and CVD associated with ML treatment.

Several important things should be known about an invasion of ML into the heart. As for frequency, PCL is rare, but ML is the third most common malignancy involving the heart. The presence of a heart lesion of ML often presents with heart-related symptoms and findings such as chest pain, HF, and arrhythmias. Notably, HF and arrhythmias can be fatal. Therefore, close examination of the heart by echocardiography, CT, and MRI is warranted to detect the heart lesions of ML when symptoms or signs of cardiac involvement of ML are observed. The identification of heart lesions of ML will result in appropriate management and survival improvement.

The frequency and types of CVD, treatment, and follow-up planning should be identified before starting treatment. Additionally, identifying patient's risk factors is necessary before treatment. This identification and plan will allow an understanding of the risk of developing CVD and appropriate management and follow-up. Appropriate assessment may reduce CVD and allow patients with ML to complete their treatments free from CVD and improve survival.

In clinical practice, it is important to keep in mind that cardiac issues in patients with ML should be identified, assessed, and managed before initiating treatment.

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