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REVIEW

Cardiotoxicity in the Childhood Oncological Therapies

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SUMMARY

Thoracic radiotherapy is frequently applied for the treatment of mediastinal tumors, lymphomas, thymoma, and lung cancers. The incidence of complications following antineoplastic therapies is associated with the incidence of cancers and the rate of prolongation of survival. Cardiotoxicity is one of the most critical complications and may occur during treatment or after years over the treatment period. Clinical pictures progressing into heart failure may occur. Radiation therapy to the thoracic region as well can be cardiotoxic. Major factors that increase the risk of cardiotoxicity in radiotherapy procedures include radiotherapy dose, anatomic regions it is applied to and accordingly the dose affecting the heart. Although cardiac adverse events during radiotherapy have been tried to be reduced by use of modern techniques for cardiac protection such as dividing the total dose among regions, reducing fractional doses, and applying apical or subcarinal block, cardiac risk increases during radiotherapy applied at a total dose of >30 Gy, concurrent or sequential application of radiotherapy and anthracyclines enhances the risk of cardiotoxicity. Late cardiotoxic effects should be kept in mind because early management of these effects may substantially prolong patient survival.

Keywords: Cardiotoxicity; chemotherapy; radiotherapy; survival.

Introduction

The incidence of complications following antineoplastic therapies is associated with the incidence of cancers and the rate of prolongation of survival. Cardiotoxicity is one of the most critical complications and may occur during treatment or after years over the treatment period. Clinical pictures progressing into heart failure may occur. Radiation therapy to the thoracic region as well can be cardiotoxic. Thoracic radiotherapy is frequently applied for the treatment of mediastinal tumors, lymphomas, thymoma, and lung cancers. Moreover, it is known that concurrent use of anthracyclines and radiotherapy contributes to cardiotoxicity. The risk of developing cardiac complications depends on cumulative anthracycline dose, presence/absence of concomitant heart disease, dose of radiation therapy to the chest wall, and patient age and gender.[1-7]

Although pericardium is involved most frequently within the clinical spectrum of radiotherapy-associated cardiotoxicity, myocardium, endocardium, papillary muscles, cardiac valves, conduction system, and epicardial coronary arteries are also involved. Based on the literature, the incidence of asymptomatic myocardial injury during long-term follow-up of pediatric patients receiving oncological therapy is between 18% and 57%, and cardiac injury occurs in approximately 5% of pediatric patients. In addition to the direct toxic effect of radiotherapy, it is known that hypothyroidism occurring in more than 90% of the patients receiving "mantle" radiotherapy leads to depression in the systolic and diastolic functions of the

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heart and forms a basis for atherosclerosis by means of influencing cholesterol mechanism.[3-7]

Major factors that increase the risk of cardiotoxicity in radiotherapy procedures include radiotherapy dose, anatomic regions it is applied to and accordingly the dose affecting the heart. Although cardiac adverse events during radiotherapy have been tried to be reduced by use of modern techniques for cardiac protection such as dividing the total dose among regions, reducing fractional doses, and applying apical or subcarinal block, cardiac risk increases during radiotherapy applied at a total dose of >30 Gy, concurrent or sequential application of radiotherapy and anthracyclines enhances the risk of cardiotoxicity. The degree of myocardial injury in the endomyocardial biopsy specimens of the patients that underwent radiotherapy and received doxorubicin at a cumulative dose of 200-300 mg/m² was equivalent to that in the patients received doxorubicin at a total dose of 400-500 mg/m² without radiotherapy. Although the left ventricle and a part of the right atrium are preserved through pericardial blocks during "mantle" radiotherapy technique, which is performed for curative purpose in the treatment of supradiaphragmatic Hodgkin lymphoma, the dose that received by the heart is >15 Gy. It is defended that cardiac morbidity can be eliminated by decreasing the size of cardiac section remaining within the site of radiotherapy using subcarinal block; however, studies performed with larger patient series in childhood are lacking. In addition to the mediastinal radiotherapy implementations, the size of cardiac section remaining within the treatment area is affected also during spinal radiotherapy, which is performed for the treatment of central nervous system tumors. The left ventricular wall thickness and ventricular end-diastolic diameter are decreased because of asymmetric distribution of radiation in the heart in growth period.[1-7]

Pericardial Disease

Acute pericarditis during radiotherapy is an uncommon situation. It is generally seen together with large mediastinal tumors and is characterized by chest pain, fever, and ECG changes. Radiotherapy does not lead to pericardial injury in the long term, thus does not require treatment discontinuation.

Subacute pericarditis is usually seen in the 1st year after radiotherapy. Symptoms and signs resemble nonspecific pericarditis. Its incidence is 10-15% in the Hodgkin lymphoma patients receiving radiotherapy at a dose of >40 Gy. It is considered that radiation-induced capillary injury plays a role in the pathogenesis of pericardial injury.[6,7]

Myocardial Disease

Radiotherapy-induced myocardial dysfunction is generally mild and subclinical. Depending on the site of radiotherapy, the right cardiac atrium and ventricle are the regions affected most by radiotherapy. Symptomatic myocardial dysfunction occurs with the doses of >60 Gy. Myocardial depression is increased when radiotherapy is performed together with anthracyclines, and total drug dose is recommended not to exceed 300–350 mg/m² in such group of patients.[4-6]

Coronary Artery Disease

Long-term follow-up of Hodgkin lymphoma patients receiving radiotherapy has shown that radiotherapy increases the risk of coronary artery disease. The risk is higher in the patients that had received radiotherapy in childhood and at total doses of >42 Gy. The risk of coronary artery disease secondary to radiotherapy is associated with total and fractionated doses. The risk increases at total doses of >40 Gy and daily doses of >200 cGy received in childhood. Usually the right and the left main coronary arteries and the left anterior descending artery are involved.[4-7]

Valvular Heart Disease

Although valvular thickening is a common condition after mediastinal radiotherapy, clinically significant valvular dysfunction is rarely encountered. The most common pathologies include combined aortic stenosis and regurgitation and mitral regurgitation.

Conduction System Defects

Although sinus node dysfunction, atrioventricular block, and non-specific ECG changes have been reported in the early period following radiotherapy, serious clinical arrhythmia is rarely encountered. Atrioventricular block in the late period after radiotherapy has been reported with doses of >40 Gy.[4-7]

Since the symptoms and signs appear quite lately, routine diagnostic examination is mandatory. ECG, chest X-ray, and echocardiography during and after

oncological therapy are among the standards. Cardiotoxicity determined during treatment period may require discontinuation or dose reduction of anthracycline therapy. In the late period of cardiac dysfunction, chest X-ray is beneficial in diagnosing heart failure, cardiomegaly, and pulmonary edema. The 12-lead ECG is frequently used as it is non-invasive and applicable anywhere. Holter monitoring is important in identifying the changes in heart rate and rhythm and in diagnosing cardiac pathologies. It is thought that abnormalities detected by Holter monitoring may be a sensitive method in detecting cardiac dysfunctions in the patients with unremarkable echocardiographic and scintigraphic examination. Echocardiography as well is frequently used as it is a non-invasive method. Systolic and diastolic functions, anatomic measurements, and "afterload" can be evaluated by echocardiographic parameters. Among these parameters, the left ventricular end-diastolic diameter, left ventricular posterior wall thickness, EF, FS, velocity of shortening, end-systolic wall stress, "afterload," and ventricular muscle mass are used in evaluating cardiotoxicity secondary to anticancer therapy.[4-9]

Cardiomyopathy and Ozone Therapy

Doxorubicin (Dox) can cause various toxic effects and the most common is the dose-dependent cardiotoxicity. Several studies showed that Dox induces cardiac abnormalities in a significant number of patients. In these studies, the authors showed that doxorubicin-induced dilated cardiomyopathy (DCM), cardiac muscle wasting, and congestive heart failure in a significant amount of patients. Induced DCM which causes oxidative stress and cardiomyocyte death is the main limitation of chemotherapy.[4-9]

The cellular injury induced by doxorubicin acts by the intermediary iron-anthracycline complex by generating free radicals causing serious damage due to oxidative stress and therapeutic strategies about increasing cellular endogenous defense systems have been identified as a good defense mechanism against oxidative stress-associated diseases such as cardiomyopathy. Several studies show that antioxidant enzymes, nitric oxide pathways, and other subcellular activities can be modulated by low doses of ozone and this approach can support the effects of ozone therapy in many pathological conditions such as diabetes mellitus, hepatic and renal ischemia-reperfusion injuries, Parkinson's disease, and coronary artery disease. More recent pharmacological findings show that ozone can also be considered as a pro-drug which, at non-toxic doses, can induce a rearrangement of the biochemical pathways.[10-13]

In a study by Delgado-Roche et al. in Sprague-Dawley rats, it was shown that ozone improved doxorubicin-induced dilate cardiomyopathy in rats and ozone therapy preserved left ventricle morphology, accompanied by a reduction of the serum pro-BNP levels. A significant increase of antioxidant enzyme activities and also a reduction of lipid and protein oxidation ($p<0.05$) were also reported in the study.[14]

In a recent review by Clavo et al.[15] which was conducted in 2019, including 13 peer-reviewed original articles about mainly four drugs (cisplatin, methotrexate, doxorubicin, and bleomycin) and their effect on cardiac functions and other organ functions such as kidney and testicles, it was shown that modulation of free radicals and antioxidants by ozone therapy was also associated with decreased chemotherapy-induced toxicity and addition of ozone was able to decrease functional and histopathological damage in the kidneys, heart, skin, and testicles.

Conclusion

There is no official guideline on the monitoring of cardiotoxicity after oncological therapy in pediatric patients. Some authors recommend echocardiographic examination in the 3rd, 6th, and 12th months after discontinuation of anthracycline therapy. The frequency of cardiac function monitoring should depend on the risk of developing cardiac complications, the child's age during antineoplastic therapy, dose of anthracycline therapy, and implementation of combined therapy. Appearance of cardiomyopathy symptoms after oncological therapy indicates poor prognosis and that it is a progressive disease. Treatment can only reduce the symptoms and disease progression. Circulatory system needs to be evaluated once in every 5 years in children over the age of 5 years receiving radiotherapy at a dose of <30 Gy.

The risk of antineoplastic therapy to be harmful for cardiac muscle is increasing because of continuously increasing cancer incidence, utilization of more aggressive therapeutic methods, and prolonged patient survival due to cancer treatment. Therefore, late cardiotoxic effects should be kept in mind because early management of these effects may substantially prolong patient survival and comfort.

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