



DERLEME / REVIEW

Cardiac and pulmonary late side effects after Hodgkin lymphoma

Hodgkin lenfoma sonrası kardiyak geç yan etkiler

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Abstract

Current treatment of childhood cancers has developed as a risk-oriented approach considering clinical, biological, genetic factors and treatment response. Cardiac diseases are the most common cause of non-cancer death in long-term childhood cancer patients. Cardiomyopathy, congestive heart failure, pericardial effusion, constrictive pericarditis, coronary artery disease, myocardial infarction, and arrhythmias may develop with the toxic effects of chemotherapy and radiotherapy. Pulmonary complications such as radiation pneumonitis, pulmonary fibrosis and spontaneous pneumothorax, which are seen in previous years due to high dose radiotherapy are currently rarely seen. Long-term follow-up of patients who are treated with mediastinal radiotherapy and/or cardiotoxic agents, such as patients with Hodgkin lymphoma, is of vital importance. Left ventricular and heart valve functions should be monitored by echocardiography, QTc and rhythm abnormalities should be monitored by electrocardiography and other factors that may affect cardiovascular health and pulmonary function tests should be evaluated periodically. Computerized tomography angiography has a role of in the early identification of possible coronary abnormalities in Hodgkin lymphoma patients at risk for coronary artery disease due to the treatments they received, especially mediastinal radiotherapy.

Keywords: Cardiac late effects, pulmonary late effects, Hodgkin lymphoma, children

Öz

Günümüzde çocukluk çağı kanserlerinin tedavisi, klinik, biyolojik, genetik faktörler ve tedaviye yanıtı dikkate alınarak risk odaklı bir yaklaşım olarak gelişmiştir. Uzun dönem çocukluk çağı kanseri hastalarında kalp hastalıkları kanser dışı ölümlerin en sık nedenidir. Kemoterapi ve radyoterapinin toksik etkileri ile kardiyomiyopati, konjestif kalp yetmezliği, perikardiyal efüzyon, konstriktif perikardit, koroner arter hastalığı, miyokard enfarktüsü ve aritmi gelişebilir. Önceki yıllarda yüksek doz radyoterapiye bağlı olarak görülen radyasyon pnömonisi, pulmoner fibrozis ve spontan pnömotoraks gibi akciğer komplikasyonları günümüzde nadiren görülmektedir. Hodgkin lenfoma hastaları gibi mediastinal radyoterapi ve/veya kardiyotoksik ajanlarla tedavi edilen hastaların uzun süreli takibi hayati öneme sahiptir. Sol ventrikül ve kalp kapak fonksiyonları ekokardiyografi ile, QTc ve ritim anormallikleri elektrokardiyografi ile izlenmeli, kardiyovasküler sağlığı etkileyebilecek diğer faktörler ve solunum fonksiyon testleri periyodik olarak değerlendirilmelidir. Bilgisayarlı tomografi anjiyografi, aldıkları tedaviler ve özellikle mediastinal radyoterapi nedeniyle risk altında olan Hodgkin lenfoma yaşayanlarında olası koroner anormalliklerin erken teşhis edilmesinde önemli bir role sahiptir.

Anahtar kelimeler: Kardiyak geç etkiler, pulmoner geç etkiler, Hodgkin lenfoma, çocuklar

INTRODUCTION

Today, with modern diagnosis and treatment approaches, general life rates in Hodgkin lymphoma (HL) are higher than 95% in low risk disease and

90% in high risk patients^{1,2}. Even in advanced stage disease, disease-free survival rates in various series are reported to be 77-92% and overall survival rates are reported as 86-100%. In most of the patients

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who developed relapse, this condition is seen in the first 3 years, but relapses have been reported 10 years after the diagnosis. Treatment regimens can be accomplished in close to half of patients with recurrence, whereas treatment-related toxicity is a major problem. Although there is no consensus on autologous bone marrow transplantation, it is reported that this method should be preferred in relapsed HL or in patients who are resistant to primary therapy².

Cardiovascular side effects on children and adolescents was first described in 1975 by Gilladoga et al. 9 of 110 children with a cumulative dose of 550 mg/m² doxorubicin or daunoubisin developed severe cardiomyopathy and heart failure³. Shortly after, Brosius et al. found radiation-related cardiac damage in all necropsy materials of 16 cancer patients diagnosed in childhood or young adulthood and given cardiac radiation over 35 Gy and severe stenosis in at least one coronary artery in six patients⁴.

Cardiac diseases are the most common cause of non-cancer death in long-term childhood cancer patients⁵. Another importance of cardiac toxicity in childhood is the decrease in quality of life of many children who respond to treatment due to acute or chronic cardiovascular diseases and limiting subsequent treatment options due to cardiotoxicity.

Current treatment of childhood cancers has developed as a risk-oriented approach considering clinical, biological, genetic factors and treatment response. Most treatment protocols still include cytotoxic chemotherapy and radiation, while a small number contain new biological and molecularly targeted agents. Dose-related toxicity studies of chemotherapeutic agents and radiation have guided the current protocols for risk.

Nowadays, the aim is to treat cancer by providing a balance that protects the health and function of normal tissues. For example, in the 1970s, the use of 300 mg/m² anthracycline (for 6-8 cycles) was available on the other hand in the 1980s, anthracycline cumulative dose of 200 mg/m² for low-risk patients and 300 mg/m² for high-risk patients was used. Again in the 1960s in mantle-type irradiation of 35-44 Gy doses were used and in the 1970s 15-25 Gy began to be used. In the 2000s, the use of radiotherapy only in selected cases was discussed in low-to-medium-risk patients, even in high-risk patients who were in complete remission

with chemotherapy⁷.

CHEMOTHERAPY AND CARDIOTOXICITY

Combined chemotherapies of less toxic agents and low-dose involved field radiotherapy have recently become the preferred treatment modality in the treatment of HL. The drugs used in multi-drug chemotherapy protocols should be effective against the tumor, antineoplastic mechanisms should be different and their toxicity should not be added to each other². Although the success rates of multi-agent chemotherapy applications are high, acute side effects caused by suppression of bone marrow and cardiotoxic, pulmonary and gonadal long-term side effects and secondary leukemia risk are negative effects of treatment. Anthracyclines are chemotherapeutic agents that are prominent in terms of cardiotoxicity in both childhood cancers and adult-onset cancers. Other chemotherapeutics known to be cardiotoxic except anthracyclines include cyclophosphamide, cytarabine, cisplatin, ifosfamide, paclitaxel and 5-fluorouracil⁸.

RADIOTHERAPY AND CARDIOTOXICITY

By the 1980s, 35-44 Gy radiotherapy application was replaced with 15-25 Gy low dose radiotherapy given to the involved areas due to significant late side effects. In the involved field radiotherapy, as well as lymph nodes that are thought to be clinically enlarged or involved, other lymph nodes in the region are also irradiated. In mantle type radiotherapy which is frequently used in treatment, submandibular, submental, cervical, supraclavicular, infraclavicular, axillary, mediastinal and pulmonary hilar lymph nodes are also included in the irradiation area. The approach adopted in the treatment of pediatric HL is low dose and involved area radiotherapy in combination with multiple agent chemotherapy regimens according to the patient's risk group. In this way, low dose radiotherapy was possible with combined chemoradiotherapy programs and high local control rates could be achieved.

Changes in the organs exposed to radiation can be classified in three groups: epithelium, parenchymal tissues, stroma and blood vessels. The narrowest vessels are also the most radiosensitive ones. This is

due to the high radiation sensitivity of the endothelial cells. Electron microscopy of the vessels in the kidney, lung and heart tissues in mammals showed irregularity of the cytoplasm, the occurrence of pseudopods and frequently cytoplasmic swelling of the lumen, separation of the endothelial cells from the basal lamina, cell picnosis, disintegration of the plasma membrane, thrombosis and rupture of the capillary wall⁹. Cardiovascular effects, which may be caused by radiation therapy in HL patients, are also related to the dose, volume and fraction of radiation. The risk of cardiac involvement in mantle type or cardiac radiotherapy above 40 Gy has been reported as 16% and risk of coronary artery disease as 10.4% in the first 20 years¹⁰. In patients who received mediastinal radiotherapy, constrictive pericarditis, aortic and mitral valve insufficiency, conduction defects and coronary artery disease may occur. Additionally a large number of asymptomatic patients may exhibit aortic valve disease, decreased systolic functions, pericardial disease, diastolic dysfunctions and stress-induced ischemia findings¹¹.

CARDIAC LATE EFFECTS

The true incidence of cardiovascular diseases in patients receiving HL treatment is unknown. Cardiomyopathy, congestive heart failure, pericardial effusion, constrictive pericarditis, coronary artery disease, myocardial infarction, and arrhythmias, which may develop with the toxic effects of chemotherapy and radiotherapy, form cardiac late side effects. It is stated that the risk of cardiac disease increases over time and increases to the highest level in 5-10 years after HL treatment. Among these, coronary artery disease, conduction abnormalities, ventricular dysfunction, valve disease and pericardial disease can be seen. It has been found that the risk of developing congestive heart failure in adulthood is 15.1 times and risk of developing coronary artery disease is 10.4 times higher in patients who have been treated for cancer in childhood¹². Late subclinical cardiovascular side effects caused by treatment are particularly evident in the third and fourth decades². The most accused agents in the development of cardiovascular complications are anthracyclines, alkylating agents and vinca alkaloids. Cyclophosphamide is also known to increase cardiac damage caused by anthracyclines and radiation.

In adults, the incidence of congestive heart failure increases with the increase in cumulative

anthracycline doses above 550 mg/m²¹³. Anthracycline group chemotherapeutics include doxorubicin (adriamycin), daunorubicin and epirubicin. It has been shown that adriamycin, frequently used in HL treatment protocols, induces apoptosis in cardiomyocytes and endothelial cells, resulting in cardiomyopathy and vasculopathy¹³. In some studies, it has been suggested that cardiotoxic effects may occur in conventional doses of adriamycin, and it has been suggested that epirubicin is an agent that can be used in place of adriamycin and may produce fewer cardiac side effects without compromising clinical efficacy¹⁴. While sinus tachycardia and supraventricular tachycardia are common, complete block, ventricular tachycardia and sudden death are rare acute complications. Congestive heart failure can be seen in acute or late period. It is known that mediastinal radiation and other chemotherapies reduce the cardiotoxicity threshold. For these reasons, long-term follow-up of patients treated with adriamycin-containing regimens and radiotherapy should be performed². Early onset coronary artery disease and acute myocardial infarction have been reported in HL patients treated in childhood¹⁵.

The risk factors for cardiovascular disease in patients who have been treated for HL, such as age, obesity, hypertension, tobacco use, family history, abnormal lipoprotein levels as well as cumulative anthracycline dose and mediastinal radiotherapy and dose should be taken into consideration.

In our late effect study related with the subject, we found that all of our patients were asymptomatic and coronary artery anomalies were detected in 19 (16%) of 119 patients. In this study, we found that receiving radiotherapy to mediastinum increased the risk of coronary artery abnormalities by 8.7 times compared to those treated without mediastinal radiotherapy¹⁶. In addition, our study was the first large prospective study in which coronary arteries were evaluated by using computed tomography angiography (CTA) in HL patients. For the first time, the role of CTA in the early identification of possible coronary abnormalities in HL patients at risk for coronary artery disease due to the treatments they received, especially mediastinal radiotherapy, was demonstrated with this study. CTA is also important to detect congenital or acquired cardiovascular anomalies which are asymptomatic but may be risky in patients' later lives¹⁷.

PULMONARY LATE EFFECTS

Complications such as radiation pneumonitis, pulmonary fibrosis and spontaneous pneumothorax, which are seen in previous years due to high dose treatments, are rarely seen. ABVD-related toxicity depends on bleomycin or doxorubicin-associated radiation-recall pneumonia. The frequency of symptomatic pulmonary dysfunction decreased with the reduction of bleomycin doses¹⁸. Asymptomatic pulmonary side effects are reported with radiotherapy and ABVD protocol widely used in HL¹⁹. Pulmonary veno-occlusive disease is also rarely seen and is associated with bleomycin. Some of them are mistakenly diagnosed with pulmonary fibrosis²⁰. Bossi et al. found increased risk of pulmonary sequelae in patients who received more intensive chemotherapy and/or radiotherapy. Pulmonary dysfunction and diffusion capacity deterioration were found especially in those who received more than 3 blocks of ABVD and more than 20 Gy of radiotherapy²¹.

The small age of the patient in terms of impairment of lung function also poses a risk²². The development of alveoli continues until 8 years of age and a negative effect during this development leads to increased risk of side effects. Pulmonary function peaks at 21 years of age and then gradually decreases. In a study conducted with 65 pediatric HL patients, pulmonary symptoms were found to be low, and a significant number of patients had subclinical dysfunction²³. Radiation-related lung injury depends on the volume of the lung tissue irradiated, the total dose given and the fractionation scheme. The late phase of injury is characterized by pulmonary fibrosis and is usually asymptomatic. Dyspnea and nonproductive cough are prominent in symptomatic patients²⁴. In the study of Oğuz et al., 13% of 75 patients with lymphoma were found to have abnormalities in pulmonary function tests (PFTs) and 23 patients who received radiotherapy were reported to have lower values than 52 patients who received only chemotherapy²⁵. Restricted pulmonary disease is the most common finding in long-term follow-up of HL patients who have been treated in most childhoods and in some studies obstructive pulmonary disease has been reported²⁶.

CONCLUSION

Long-term follow-up of patients who are treated with mediastinal radiotherapy and/or cardiotoxic

agents, such as patients with HL, is of vital importance. Left ventricular and heart valve functions should be monitored by echocardiography, QTc and rhythm abnormalities should be monitored by electrocardiography and other factors that may affect cardiovascular health and PFT should be evaluated. In terms of the frequency of these scans, the history, the findings from the physical examination, the age of the patient, the time after treatment, the degree of exposure to radiation and the cumulative dose of drugs should be guiding.

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