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Cardiovascular involvement in blood cancers: ALL, AML, CLL, and CML

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Abstract
Global cancer statistics will continue to grow in the coming years. Leukemia is the fifth leading cause of death in the world and the second one in Iran; therefore, it is very important to study the affected areas, including the cardiovascular system in this disease. In heart cancer, tumors whose primary origin is the heart are called primary tumors, which are very rare. Tumors that originate in other parts of the body and spread to the heart are called secondary tumors. Although heart cancer is still rare, most cancers found in the heart come from other parts of the body and are considered as secondary tumors. The symptoms of metastatic heart cancer vary and depend on the location and extent of the lesion. Cancer can also affect the heart in other ways. One of these ways is the effect of the treatments used, which is reported among acute lymphocytic leukemia, acute myelogenous leukemia, chronic lymphocytic leukemia, and chronic myelogenous leukemia due to the use of tyrosine kinase inhibitors as the main drug in reducing mortality among these patients. Pericardial involvement is reported to be the most common cardiovascular complication of drug use among different kinds of leukemias. In this article, we try to collect cardiovascular evidence related to acute lymphocytic leukemia, acute myelogenous leukemia, chronic lymphocytic leukemia, and chronic myelogenous leukemia, separately.
Keywords: Acute lymphocytic leukemia, Acute myelogenous leukemia, Cancer, Cardiovascular disease

Introduction

Cancer is a widespread disease that is not related to a specific time and place. As it is the second leading cause of death in the world and the third in Iran, it is of great importance (1). Global cancer statistics will continue to grow in the coming years (1). Leukemia is the fifth leading cause of death in the world and the second one in Iran; therefore, it is very important to study the parts involved in this disease (2). Meanwhile, acute myeloid leukemia is the second most common leukemia and the third deadliest leukemia in Iran (3). There are many types of leukemia. Some types of leukemia are more common in children (4). Other forms of leukemia are more common in adults. Leukemia is a cancer of the body's hematopoietic tissues, including the bone marrow and lymphatic system (5). Leukemia usually involves white blood cells. White blood cells strongly fight infections in the body (6). White blood cells grow and divide naturally in a healthy person and the body needs them. But in people with leukemia, the bone marrow causes abnormal white blood cells, which do not function properly (7). Major types of leukemia include the following (8):

- Acute lymphocytic leukemia (ALL) is the most common type of leukemia in children but also occurs in adults.
- Acute myelogenous leukemia (AML) is another type of leukemia that occurs in children and adults. But it is the most common type of acute leukemia in adults.
- Chronic lymphocytic leukemia (CLL) is the most common chronic leukemia in adults and the patient

may feel well for years without treatment.

- Chronic myelogenous leukemia (CML), which mainly affects adults. A person with CML may have few or no symptoms for months or years.

Other types of leukemia include hairy cell leukemia, myelodysplastic syndromes, and myeloproliferative disorders, which are seen rarely (9). In heart cancer, tumors whose primary origin is the heart are called primary tumors, which are very rare (10). Tumors that originate in other parts of the body and spread to the heart are called secondary tumors (11). Although heart cancer is still rare, most cancers found in the heart come from other parts of the body and are considered as secondary tumors (12). The symptoms of metastatic heart cancer vary and depend on the location and extent of the lesion (13). Cancer can also affect the heart in other ways. One of these ways is the effect of the treatments used, which is reported among ALL, AML, CLL, and CML due to the use of tyrosine kinase inhibitors as the main drug in reducing mortality among these patients which can be used as a treatment for chronic cardiovascular complications for the rest of patients' lives(14). In this article, we try to collect cardiovascular evidence related to ALL, AML, CLL, and CML cancers separately.

Side effects of cancer treatment on the cardiovascular system

In general, cancer treatment can cause the heart to pump less efficiently, alter blood flow, or increase the risk of blood clots (thrombosis), which can lead to a heart attack (15). The most common heart disease caused by these changes is congestive heart failure, and the most serious heart diseases related to the treatment of cancer are myocardial infarction (pericarditis) and coronary artery disease (16). Other heart problems that may develop as a result of cancer treatment include low blood pressure (hypotension), high blood pressure (hypertension), abnormal heart rhythms (arrhythmias), and valvular disease. Routine drugs commonly used to treat leukemia are tyrosine kinase inhibitors (17). The use of protein kinase inhibitors is a targeted treatment. They work by inhibiting kinase, an enzyme involved in many cellular processes (18). Kinases add phosphate groups to amino acids and are classified according to the type of amino acid they phosphorylate. For example, the addition of phosphate groups to the serine and threonine amino acids of proteins is done by the specific protein kinase of serine and threonine. The protein tyrosine kinase adds a phosphate group to the amino acid of tyrosine protein (19). This reaction affects the cellular communication signals that are responsible for cell division and growth. These kinases affect the growth factors that regulate the cell cycle. Tyrosine kinase inhibitors are used to treat leukemia (imatinib, dasatinib) and lymphoma (ibrutinib) (20).

ALL

ALL is a kind of cancer that appears in the basic precursors of white blood cells (lymphocytes) in the bone marrow (where new blood cells are produced) (21). Leukemia cells usually occupy the bloodstream rapidly and spread to other organs such as the lymph nodes, liver, spleen, central nervous system (brain and spinal cord), and testes (in men) (22). Other cancers also can start in these organs and spread to the bone marrow, but they are not considered leukemia. The word "acute" means that leukemia progresses rapidly and can lead to death within a few months if treatment is not started (23).

Cardiovascular involvement in ALL

ALL is the most common malignancy in children. However, it may rarely be associated with eosinophilia. Patients with ALL and eosinophilia have a higher prognosis and higher incidence of cardiac complications than patients with standard lymphoblastic leukemia (24). In several

cases, eosinophilia has been reported in cases of leukemia with heart disease (24). A 13-year-old boy with ALL has been reported with a defect in B precursors with symptoms of peripheral eosinophilia, chest pain, and a large mass in the left ventricle of the heart (25). He received multiple chemotherapy treatments but died 25 days later of respiratory failure (25). According to a study, a patient with acute T-cell leukemia showed a right atrial tumor (26). In this regard, cardiac involvement with hematologic malignancies should be considered. Although it is a rare clinical symptom, it can affect the treatment process (27). These patients are considered resistant to cancer treatments. Myocardial complications in patients with ALL are usually rare and are considered as secondary symptoms due to infection or chemotherapy (28). However, there have been reports of myocardial involvement in these patients with acute B-cell lymphoblastic leukemia with myocardial involvement in an elderly man (29).

Side effects of ALL treatment in children can lead to a lifelong risk of heart complications (30). Unfortunately, almost all children rescued from this disease will experience delayed post-treatment conflicts, which can lead to complications or early death (31). In a case study, a child with ALL was treated with the Inotuzumab monoclonal antibody. On the other hand, reports indicated that doxorubicin chemotherapy in children with ALL is effective in myocardial cell involvement, which according to the evidence of treatment with a free radical protector may prevent vascular complications in children treated with ALL (32, 33).

AML

In bone marrow leukemia, abnormally large amounts of blood cells are produced (34). These cells are different from normal blood cells and do not function properly. As a result, they stop producing normal white blood cells and destroy a person's ability to fight disease (35). Leukemia cells also negatively affect the production of other types of blood cells made by the bone marrow, including red blood cells, which carry oxygen to the body's tissues, and blood platelets, which prevent blood from clotting. Therefore, in different types of leukemia, there are complications such as weak immunity, anemia, and blood coagulation disorders (36). In acute leukemia, bone marrow cells do not mature properly (37). Immature leukemic cells are often called blasts that continue to reproduce and accumulate. In myeloid leukemia, the source of cancer cells is the myelocyte class, which makes red blood cells, platelets, or other white blood cells other than lymphocytes, such as granulocytes and monocytes (38). The M3 or M4 subgroup has the best prognosis (39). Some chromosomal changes, such as reverse translocation and translocation, have a better prognosis. Other chromosomal changes, such as translocation and the addition and disruption of chromosomes 5 or 7, have a worse prognosis (40). Patients younger than 55 years have a better prognosis. Primary pre-leukemic conditions or secondary leukemias that develop after treatment for another cancer, have a worse prognosis. There are different types of treatment for adults with AML (41). In the treatment of AML leukemia, four conventional therapies are used: chemotherapy, radiation therapy, bone marrow transplantation, and treatment with other drugs (42).

Cardiovascular involvement in AML

During the studies, neo-angiogenesis was observed in biopsies of children with AML (43). On the one hand, a correlation was found between the rate of new vascularization and urinary bFGF levels in AML patients (44). MMP-2 secretion also increases as bone marrow vascularization increases. MMP-9 secretion can also be increased by mononuclear and CD34 + cells (45). Evidence suggested that in some patients, VEGF levels increase, which can

be considered a prognostic factor for survival in high-risk patients (46). Myopericarditis has been reported as a rare feature of acute myeloid leukemia. Complications include reports of a 37-year-old woman with AML (47).

Cardiac hypertrophy is a complication of the treatment of AML using stem cells (48). The recurrence of heart attacks in these patients is about 2-5% and even in some cases, these complications may not be determined by clinical examinations during the patient's lifetime and after death, they are determined by pathological examinations (49). In a case report, a 24-year-old man with a history of AML was observed with complications of hypertrophy after stem cell transplantation (50).

As mentioned, heart tumors, as well as heart complications caused by malignancies such as AML, are more of a therapeutic complication (51). One of these treatments that are associated with the risk of treatment failure is the use of anthracyclines in chemotherapy, and although these drugs are a standard treatment for AML, they can also have toxic and persistent effects on patients (52).

CLL

CLL is a type of B $CD5^+$ cell malignancy characterized by the accumulation in peripheral blood, bone marrow, and secondary lymph nodes that leads to lymphocytosis, lymphadenopathy, and splenomegaly (53). Although CLL is the most common leukemia in adults in Western societies, it is less common in Asia (54). The risk of developing CLL in men is twice as high as in women, and the average age of diagnosis is about 70-72 years (55). CLL is divided into two main subsets that are clinically different. These subtypes are introduced by laboratory examination of the presence or absence of mutations in the gene encoding the variable region of the immunoglobulin heavy chain expressed in CLL cells, and this branch reflects a superficial differentiation of B cells from their origin (56). CLL can cause a variety of symptoms, including fatigue, involuntary weight loss, excessive night sweats, and fever. In general, CLL occurs in both invasive and non-invasive forms, which in the non-invasive state, does not need treatment for several years, but the invasive type needs immediate treatment (55, 57).

Cardiovascular involvement in CLL

Primary CLL cardiac malignancies are as rare as ALL and AML, and of these few, 75% are pericardial malignancies (58). One report cited an 83-year-old man with CLL who has been suffering from dyspnea and low blood pressure for 10 years (59). Blood tests and electrocardiograms showed acute myocardial infarction. The disease deteriorated rapidly, and shortly thereafter, the patient died. An autopsy revealed severe coronary atherosclerosis and left ventricular myocardial infarction (60). Pathological examination showed that CLL could affect lymph nodes, liver, spleen, intestine, and kidney (60). In another report, a 58-year-old African-American woman with a history of traveling to Nigeria and having a positive tuberculin skin test was referred to a medical center with a heart disorder (61). Other complications include mild fever, lymphocytosis, and bloody pericardium (61). Evaluation of blood using flow cytometry and pericardial biopsy by immunohistochemistry showed CD5 (+) and CD20 lymphocytes in both tissues, indicating CLL that manifested itself in the early stages with these symptoms (61). Among pericarditis complications, obstructive pericardial involvement accounts for 4% of CLL pericardial involvement, which is reported in a 57-year-old man with CLL with acute cardiorespiratory failure due to hyperleukocytosis (62). Although acute pulmonary insufficiency due to leukemia

is a known finding for patients with AML or CML, it is rare in CLL (63, 64).

Chronic Myeloid Leukemia (CML)

CML is a proliferative disease in which, mainly, the granulocyte cell line is increased and is accompanied by platelet hyperplasia and erythroid lineage simultaneously (65). The unique feature of this disease among myeloproliferative neoplasms is its clinical course, which in all cases turns into acute leukemia (66). CML is the first malignant blood disease to be associated with a specific chromosomal abnormality (66). In more than 95% of patients, a colony proliferation of a stem cell with the Philadelphia chromosome is seen. In this case, a balanced shift occurs between chromosomes 9 and 22(66). This mutation binds the ABL gene on chromosome 9 to chromosome 22, resulting in a new cancer gene called BCR-ABL (66). The BCR-ABL product is a spontaneously active cytoplasmic tyrosine kinase that causes leukemia in hematopoietic cells (66). The BCR-ABL fusion protein activates a group of message transmission mechanisms that allow cells to grow independently of the regulation of cytokines and the effect of bone marrow stroma. It also makes CML cells resistant to chemotherapy and protects against programmed cell death (apoptosis) (67).

Cardiovascular involvement in CML

According to a Swedish study, the risk of arterial and venous thrombosis is higher among patients with CML than in the general population (68). Based on this study and other similar studies, such patients with cardiovascular involvement have been treated with one of the tyrosine kinase inhibitors (68). Reports also indicated that patients treated with one of the second-generation TKIs, nilotinib or dasatinib, have a higher risk of myocardial infarction than patients treated with imatinib(69). A case report suggested that nilotinib may cause vasospasm, which in turn may trigger peripheral arterial occlusion (70). Although the information suggested that CML is associated with cardiovascular disorders, as mentioned, these disorders can be affected by different treatments and cause a variety of symptoms (71). In addition, because the cardiovascular symptoms of CML treatment can coincide with the diagnostic symptoms, it will be difficult to differentiate these symptoms completely, and despite the development of TKIs tyrosine kinase inhibitors has changed the therapeutic perspective for many different cancers, including CML, dramatically and patient survival has increased significantly, but in some cases, this deadly cancer can be controlled as a chronic disease (72-74).

Conclusion

As mentioned, cardiovascular disorders in blood cancers are not related to primary tumors, and secondary tumors, as can be seen from the reports, are occasionally metastatic. But what is very important is the side effect of tyrosine kinase inhibitors. Although the success of TKIs in treating leukemia is still unique, there are indications that these drugs have a side effect on the cardiovascular system. This has posed a challenge to medical oncology, so that treatment with tyrosine kinase inhibitors, although it can quickly save patients' lives over a period of time, in some cases, can cause chronic complications for the patient for the rest of his life.

Conflicts of interest

There are no conflict of interest in this research.

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