Review

Atrial Fibrillation in Hematologic Malignancies, Especially After Autologous Hematopoietic Stem Cell Transplantation: Review of Risk Factors, Current Management, and Future Directions

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Abstract

Atrial fibrillation (AF) is the most common cardiac arrhythmia and is associated with significant morbidity and mortality worldwide. In addition to well-established risk factors, cancer has been increasingly associated with the development of AF. Its increased occurrence in those with hematologic malignancies has been attributed to chemotherapeutic agents and autologous hematopoietic stem cell transplantation (AHSCT). Recently, a few studies have attempted to define the etiopathogenesis of AF in hematologic malignancies. The management of AF in these patients is challenging because of the concurrent complicating factors, such as thrombocytopenia, orthostatic hypotension, and cardiac amyloidosis. More studies are needed to define the management of AF, especially rate versus rhythm control and anticoagulation. Arrhythmias, in particular, AF, have been associated with an increased length of stay, increased intensive care unit admissions, and greater cardiovascular mortality. In the present review, we describe AF in patients with hematologic malignancies, the risk factors, especially after AHSCT, and the current management of AF.

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AF in Hematologic Malignancies

Review of Risk Factors and Current Management

Atrial fibrillation (AF) is the most common cardiac arrhythmia and results in significant morbidity and mortality worldwide. In addition to the well-known and established risk factors of AF, such as increasing age, male gender, hypertension, valvular heart disease, hyperthyroidism, diabetes, congestive heart failure, chronic obstructive pulmonary disease, malignancy, and cancer have been increasingly associated with the development of AF.[1] AF has also recently been associated with occult cancer.[2] Although the association with cancer in epidemiologic studies has generally been limited, AF has been seen in an increasing trend with hematologic malignancies, especially with the use of chemotherapeutic agents such as anthracycline derivatives, high-dose melphalan, and chemotherapy regimens with autologous stem cell transplantation. The causes of this trend are multifactorial.[1-3] In the present review, we describe the role of AF in hematologic malignancies, especially after autologous hematopoietic stem cell transplantation (AHSCT), and the management of AF.

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Incidence of AF

No study, to the best of our knowledge, has been performed to determine the prevalence of AF in those with hematologic malignancies. Several retrospective studies of this population during or after chemotherapy have been performed,[3-7] and AF has been implicated to have an increased prevalence in the presence of non-Hodgkin lymphoma and multiple myeloma, especially after high-dose chemotherapy and AHSCT. Olivieri et al,[5] in 1998, first described paroxysmal AF after high-dose melphalan in 5 patients with AHSCT with blood progenitor cells. Of these 5 patients, 3 had multiple myeloma and 2 had non-Hodgkin lymphoma.[5] Subsequently, Hidalgo et al[7] studied the occurrence of supraventricular tachyarrhythmias after AHSCT and reported a prevalence of 4.1% in their study group, which was considered an underestimation. In their study, AF was the most common arrhythmia, and non-Hodgkin lymphoma was the most common malignancy

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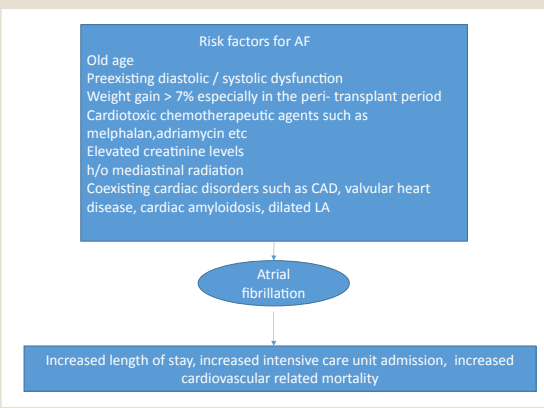
associated with it.[7] They also found that AF was more common after AHSCT than after allogenic stem cell transplantation.[7]

Singla et al[8] studied the incidence and risk factors for cardiac arrhythmias during AHSCT. They found that supraventricular arrhythmias were present in approximately 9%, and AF was the most common arrhythmia, present in 7% of the study population. The most common indication for AHSCT was plasma cell disorders.[8] With AHSCT becoming the standard therapy for patients with plasma cell disorders, especially multiple myeloma, AF has been increasingly recognized in this population.[8-10] Fatema et al[11] reported an incidence of 10% for AF in patients with multiple myeloma undergoing AHSCT. In addition, at our institution, Sureddi et al[9] studied the incidence of AF after AHSCT in patients with multiple myeloma. In that study, all the patients with multiple myeloma who had undergone AHSCT and developed AF were identified from January 2000 to December 2009 using the "International Classification of Diseases, 9th revision," codes for multiple myeloma, AF, and AHSCT. A total of 769 patients with multiple myeloma, AF, and AHSCT were found. Of these 769 patients, 278 patients were inpatients and were included in the present study. Of the 278 patients, 75 (27%) developed AF after AHSCT. AF developed after a mean duration of approximately 14.8 days. The main risk factors associated with AF were left ventricular dysfunction, renal dysfunction, left atrial enlargement, and hypertension.[9] However, most of the stem cell transplantations at our institute are performed as outpatient procedures.[9] Recently, AF has also been observed as a marker of occult malignancy. Ostenfeld et al[2] reported an association of AF with many solid organ tumors and hematologic malignancies such as non-Hodgkin lymphoma.

Most recently, Tonorezos et al[3] reported that AF is the most common type of arrhythmia associated with hematopoietic transplants in patients with hematologic malignancies. Also, the development of arrhythmias, in particular AF, has been associated with an increased length of stay, increased intensive care unit admission, and greater cardiovascular mortality[12,13] (Figure 1).

Figure 1 Flow Chart Showing Risk Factors for, and Clinical Implications of, Atrial Fibrillation (AF) in Patients With Hematologic Malignancies



Abbreviations: CAD = Coronary Artery Disease; h/o = History of; LA = Left Atrium.

Risk Factors

Although the exact pathophysiology of the increased incidence of AF in the presence of hematologic malignancy is unknown, several risk factors have been identified, including high-dose chemotherapy and AHSCT. Older age and a coexisting heart condition were reported as the most common risk factors related to AF.[10,11] Also, a weight gain of $\geq$ 7% within the first week after AHSCT was associated with a significantly increased risk of developing AF and/or atrial flutter (AFL) within the first 21 days.[11] Fatema et al[11] concluded that a weight gain of $>$ 7% causes an increase in the preload, resulting in acute stretching of the left atrium and pulmonary veins, which leads to electrical remodeling and shortening of the atrial effective refractory period, predisposing the patient to atrial arrhythmia.

Diastolic dysfunction, especially with weight gain, results in a ninefold increased risk of the development of AF.[11] The ejection fraction, which is a marker of systolic function, was not much related to development of AF.[11] However, a history of hypertension, a history of coronary artery disease, any history of arrhythmia, and an increased left atrial diameter have been associated with an increased risk of AF, especially after AHSCT.[8-10] Another predisposing factor emphasized in multiple studies has been the type of chemotherapeutic agents used (with and without AHSCT). In particular, melphalan and anthracycline-based chemotherapy regimens were associated with a greater incidence of AF.[5,8,14] Recently, ibrutinib, a newer chemotherapeutic agent and the drug of choice for the treatment of relapsed or refractory chronic lymphocytic leukemia and mantle cell lymphoma, has been shown to increase the risk of AF, potentially through inhibition of cardiac phosphoinositide 3-kinase-Akt signaling.[15] It was recently reported that enhanced phosphoinositide 3-kinase (p110-α) activity can delay or prevent the progression of heart disease and that increased activity can also be beneficial.[16] Electrolyte imbalances, in particular, hypomagnesemia, have also been associated with AF in some studies.[10] Other risk factors, such as elevated creatinine levels and a history of mediastinal radiation, have also been associated with an increased risk of AF in some studies.[9,17] The risk factors are listed in Table 1.

Role of AHSCT in AF Development in Hematologic Malignancies

AHSCT has become the standard of care for many diseases of the hematopoietic system and malignancies with or without chemotherapy and/or radiotherapy. The most common indications

Table 1 Major Risk Factors for Atrial Fibrillation in Hematologic Malignancies

Old age
Pre-existing diastolic dysfunction
Weight gain $>$ 7%, especially in peritransplant period
Chemotherapeutic agents with increased cardiotoxicity such as melphalan, Adriamycin, ibrutinib
Elevated creatinine levels
h/o mediastinal radiation
Coexisting cardiac disorders, such as CAD, valvular heart disease, cardiac amyloidosis, dilated LA

Abbreviations: CAD = coronary artery disease; h/o = history of; LA = left atrium.