The risk of venous thromboembolism (VTE) in patients with cancer is several-fold higher than that in individuals without cancer. Recent studies demonstrated a high incidence of VTE in patients with hematologic malignancies as well as in patients with solid cancers. The reported incidence of VTE in lymphoma is variable, ranging from less than 5% to 59.5%. The incidence of VTE is higher in non-Hodgkin lymphoma than it is in Hodgkin lymphoma. The incidence of VTE also varies according to the disease grade, the disease stage, the performance status of the patient, and the site of disease. Most VTE cases occur at the diagnosis of cancer or early in the course of cancer treatment. An elevated incidence of VTE is also reported in cases of myeloma. VTE occurs in approximately 5% of myeloma patients treated with conventional chemotherapy, and treatment of myeloma patients with immunomodulatory drugs (IMid)-based therapy increases the risk of VTE. Prophylactic aspirin or anticoagulant is used in myeloma patients treated with IMid-based therapy. Several reports have indicated that the incidence of VTE is relatively low in Asian patients treated with IMid-based therapy, and concomitant use of bortezomib reduces the risk of VTE. The incidence of arterial thrombosis is also increased in patients with myeloma and monoclonal gammopathy of undetermined significance. Further studies are needed to develop a predictive model for identifying patients with lymphoma and myeloma who are at high risk for developing thrombosis.

Keywords: lymphoma, multiple myeloma, venous thromboembolism, arterial thrombosis

Introduction

Venous thromboembolism (VTE) is a common and serious complication in patients with cancer. The risk of VTE in cancer patients is several-fold higher than that in individuals without cancer,1,2 and VTE is the second leading cause of death in solid cancer patients undergoing chemotherapy.3 The incidence of VTE varies according to the site of the cancer, and the VTE rates in gastric and pancreatic cancer patients are 4.3-fold higher than the mean VTE rates in the cancer population.4

The association between cancer and arterial thrombosis (AT) is less well described than the association between cancer and VTE. A retrospective study of 1934 cancer patients reported a relatively low incidence of AT in ambulatory cancer patients treated with chemotherapy,5 in contrast to several studies demonstrating an increased risk of AT in patients with certain types of cancer or those receiving specific anti-cancer agents such as bevacizumab.6 Recent studies demonstrated a high incidence of VTE in patients with hematologic malignancies as well as in patients with solid cancers.7 Some studies report an increased incidence of AT in patients with hematologic malignancies.8,9 Here we present several studies, including two studies conducted at Keio University Hospital, and discuss the incidence and risk factors for thrombosis in patients with lymphoma or multiple myeloma. This article summarizes the current knowledge about thrombosis in patients with these diseases, but because of space considerations many important studies on other forms of cancer are not cited.
Lymphoma

Lymphoma is the most common hematologic malignancy worldwide, and incidences of lymphoma in Japan are 15.8 in men and 13.4 in women per 100,000 population.10 Non-Hodgkin lymphoma (NHL) is much more common than Hodgkin lymphoma (HL), and diffuse large b-cell lymphoma (DLBCL) is the most common type of lymphoma. We retrospectively analyzed the incidence of VTE in Japanese patients with DLBCL who received the first cycle of chemotherapy at Keio University Hospital. Of 142 patients analyzed in our study, 15 (11%) patients developed VTE. VTE was diagnosed either at the time of lymphoma diagnosis or during the first three cycles of chemotherapy in 13 patients. A performance status (PS) score of 2, 3, or 4 was a significant risk factor for developing VTE in our study.11

The incidence of VTE in lymphoma is variable, ranging from less than 5%2,12 to 59.5%13 (Table 1). There are several reasons for the wide incidence range. Some studies have demonstrated a relationship between the subtype of lymphoma and the incidence of VTE. Of 207 patients with lymphoma analyzed in a study by Sgarabotto et al., 4.8% of patients developed VTE. The incidence of VTE was 3.2% in HL patients and 5.6% in NHL patients. Among NHL patients, the incidence of VTE was significantly higher in high-grade disease than in low-grade disease (7.5% vs 3%).14 A meta-analysis of 29 independent cohorts involving 18,018 lymphoma patients identified 1149 thrombotic complications (959 VTE and 190 AT). The incidence of thrombosis was significantly higher in NHL than in HL (6.5% vs 4.7%). Among NHL patients, those with high-grade disease had a greater risk of thrombosis than those with low-grade disease (8.3% vs 6.3%).15 A prospective study conducted in Korea assessed 686 lymphoma patients and also demonstrated a higher incidence of VTE in NHL than in HL (8.0% vs 6.7%). VTE occurred in 8.9% of DLBCL patients within 1 year.16 A recent large-scale study using a cancer registry included 16,755 NHL patients and revealed a 2-year cumulative incidence of VTE of 2.1% for low-grade, 4.8% for interme-

<table>
<thead>
<tr>
<th>Reference</th>
<th>Disease</th>
<th>n</th>
<th>Incidence/type of thrombosis</th>
<th>Risk factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sgarabotto et al.14</td>
<td>Lymphoma</td>
<td>207</td>
<td>4.8%/VTE</td>
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<td></td>
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<td>3.2% (HL), 5.6% (NHL)</td>
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<td>7.5% (high-grade)</td>
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<td>3% (low-grade)</td>
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<td>Caruso et al.15</td>
<td>Lymphoma</td>
<td>18,018</td>
<td>5.3%/VTE, 1.1%/AT</td>
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<td>4.7% (HL), 6.5% (NHL)</td>
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<td>8.3% (high-grade)</td>
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<td></td>
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<td></td>
<td>6.3% (low-grade)</td>
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<tr>
<td>Park LC et al.16</td>
<td>Lymphoma</td>
<td>686</td>
<td>7.9% (21.8 months)/VTE</td>
<td>NHL chemotherapy brain involvement age (&gt;60 yrs)</td>
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<td>6.7% (HL), 8.0% (NHL)</td>
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<td>Khorana et al.2</td>
<td>HL</td>
<td>10,075</td>
<td>4.6%/VTE</td>
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<td>NHL</td>
<td>56,964</td>
<td>4.8%/VTE</td>
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<td>Ottinger et al.17</td>
<td>NHL</td>
<td>593</td>
<td>6.6%/VTE</td>
<td>Stage IV B-medialstinal clear cell</td>
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<tr>
<td>Mahajan et al.12</td>
<td>NHL</td>
<td>16,755</td>
<td>3.6% (1 yr), 4.0% (2 yr)/VTE</td>
<td>Advanced stage chronic comorbidities age (&gt;75 yrs) intermediate/aggressive high-grade</td>
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<td>2.1% (low-grade)</td>
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<td>4.8% (intermediate/aggressive)</td>
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<td>4.5% (high-grade)</td>
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<td>Komrokji et al.18</td>
<td>DLBCL</td>
<td>211</td>
<td>12.8%/VTE</td>
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<tr>
<td>Yokoyama et al.11</td>
<td>DLBCL</td>
<td>142</td>
<td>11%/VTE</td>
<td>PS 2 or worse</td>
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<td>Goldschmidt et al.13</td>
<td>CNS lymphoma</td>
<td>42</td>
<td>59.5%/VTE</td>
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<tr>
<td>Lekovic et al.20</td>
<td>PMBCL</td>
<td>42</td>
<td>35.7%/VTE</td>
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</table>

HL; Hodgkin lymphoma, NHL; non-Hodgkin lymphoma, DLBCL; diffuse large b-cell lymphoma, CNS; central nervous system, PMBCL; primary mediastinal large b-cell lymphoma, VTE; venous thromboembolism, AT; arterial thrombosis, IPI; international prognosis index, PS; performance status
The incidence of VTE also seems to be affected by the disease stage. In one study, VTE occurred in 6.6% of lymphoma patients, and the incidence was high in stage IV patients. In another study, 12.8% of DLBCL patients had VTE, and stage I disease was associated with a low risk, whereas a high International Prognostic Index score was associated with a high risk of VTE.

The lymphoma site is also an important factor for developing VTE. The incidence of VTE is as high as 59.5% in patients with central nervous system (CNS) lymphoma. CNS involvement is also an independent risk factor for VTE. The incidence of VTE in patients with CNS lymphoma is comparable to that of patients with other types of brain tumors. The incidence of VTE is also high in patients with primary mediastinal large b-cell lymphoma. VTE in patients with primary mediastinal large b-cell lymphoma is caused mainly by local growth of the lymphoma, resulting in mechanical compression of the veins. Consistent with our findings, most VTE cases occurred at diagnosis of cancer or early in the course of cancer treatment. These observations suggest that VTE is a frequent complication in some lymphoma patients.

Several studies report increased risk of coronary artery disease or increased mortality caused by myocardial infarction in HL patients in relation to mediastinal radiotherapy. Doxorubicin is a cardiotoxic drug often used to treat NHL patients, but the risk of cardiovascular death or cardiac complications in patients with NHL undergoing doxorubicin therapy remains unclear. Some studies have revealed an increased incidence of cardiac complications, including coronary artery disease and a relatively high risk of cardiovascular mortality, in patients with NHL. These cardiovascular mortality and cardiac complications are considered late complications of anti-lymphoma treatment. Although the risk of cardiovascular disease early in the treatment course of lymphoma is rarely described, higher risks of suicide and cardiovascular death after diagnosis of cancer, including hematologic malignancies, were recently reported. Among cardiovascular deaths, embolism or thrombosis and myocardial infarction are strongly associated with cancer. The relative risk of cardiovascular death is 8.7 in patients with hematologic malignancy compared with non-cancer patients within the first week after diagnosis. Although the relative risk decreased gradually, it remained as high as 1.2 at 1 year after the diagnosis. Further studies are needed to elucidate the incidence and risk factors of cardiac complications including coronary artery disease.

Multiple myeloma is the second most common hematologic malignancy. The number of patients with myeloma is increasing in both Western countries and Asian countries, and the incidences of myeloma in Japan are 4.0 in men and 3.5 in women per 100,000 population.

We retrospectively analyzed the incidence of VTE in patients with myeloma who were treated with induction chemotherapy followed by single or double autologous peripheral blood stem cell transplantation (ASCT) conditioning with high-dose melphalan at Keio University Hospital. Of 98 patients analyzed, 7 (7.1%) developed VTE. VTE occurred before or at ASCT in 5 patients.

VTE occurs in approximately 5% of myeloma patients treated with conventional chemotherapy in Western countries, and the incidence of VTE in our study was comparable to that in the Western population. In a large-scale study assessing the risk of thrombosis in 18,637 patients with myeloma and 5326 patients with monoclonal gammopathy of undetermined significance (MGUS), the hazard ratios of VTE at 1, 5, and 10 years after multiple myeloma diagnosis were 7.5, 4.6, and 4.1, respectively. The incidence of VTE was also increased in MGUS patients, and the hazard ratios of VTE at 1, 5, and 10 years after MGUS diagnosis were 3.4, 2.1, and 2.1, respectively.

Treatment of myeloma patients with immunomodulatory drugs (IMiD), such as thalidomide (Thal) or lenalidomide, in combination with dexamethasone and/or chemotherapy is well recognized to increase the risk of VTE in myeloma patients. The incidence of VTE increases to as high as 58% in patients receiving Thal, vincristine, doxorubicin, and dexamethasone. The incidence of VTE is higher in newly-diagnosed myeloma patients than in relapsed or refractory myeloma patients receiving IMiD-based therapy, and the efficacy of thromboprophylaxis in these patients has been evaluated by meta-analysis. The incidence of VTE in newly-diagnosed myeloma patients treated with Thal+dexamethasone is 4.1/100 patient cycles without prophylaxis, and this figure reduces to 2.6 with prophylaxis. A therapeutic dose of anticoagulant showed the largest risk reduction. None of the thromboprophylaxis agents show a clear benefit in those receiving lenalidomide-based therapy or those who received prior therapy. Prospective studies demonstrated that aspirin and warfarin are effective, as is low molecular weight heparin (LMWH), for VTE prevention in newly-diagnosed patients treated with Thal-based or lenalidomide-based therapy (Table 2), and the use of prophylactic aspirin, warfarin, or LMWH is recommended in treatment guidelines. Prophylactic aspirin is used for low-risk patients, and warfarin is used for high-risk patients receiving IMiD in Japan, because the use of LMWH in these patients is not covered by health insurance. Several reports, however, have indicated that VTE is less frequent in Asian myeloma patients receiving
Thal than in Western myeloma patients. A retrospective study conducted in Japan to assess the incidence of VTE in relapsed or refractory myeloma patients treated with Thal-based regimens revealed that only 14 (1.4%) of 1035 patients developed VTE, and treatment with or without other agents did not affect the incidence of VTE. Neither thromboprophylaxis with aspirin nor warfarin reduced the incidence of VTE in these patients. Although the sample size was small, 50 patients received Thal or lenalidomide after ASCT in our study, and VTE occurred in only 1 patient among them. Studies from Korea and from Taiwan also demonstrated a low incidence of VTE in myeloma patients receiving Thal. These observations suggest ethnic variance in the frequencies of VTE in myeloma patients treated with IMid-based regimens. Although the mechanisms underlying the thrombogenic effects of IMid are not fully understood, one recent study showed a significant increase in factor VIII and a reduction in thrombin antithrombin in patients receiving Thal-prednisone maintenance following ASCT compared to patients not receiving maintenance following ASCT.

Bortezomib (BOR) is a proteasome inhibitor, and BOR-based therapy is the most frequently used induction chemotherapy for newly-diagnosed myeloma patients. The incidence of VTE is reported to be as low as 0%–5% in newly diagnosed myeloma patients receiving IMid-based therapy with BOR, which is comparable to the incidence in those receiving conventional chemotherapy, and lower than that in patients treated with IMid-based therapy without BOR. Although the mechanism by which BOR affects the incidence of VTE is unknown, BOR reduces adenosine diphosphate-induced platelet aggregation in vitro. A recent animal study also demonstrated that transcription factor Kruppel-like factor 2 is a critical determinant of thrombosis and that the antithrombotic effects of BOR are dependent on Kruppel-like factor 2. Further experiments are needed to determine the clinical significance of these findings.

Several reports have demonstrated a high incidence of AT in myeloma patients. A prospective study evaluating the risk of AT in relatively young myeloma patients undergoing conventional induction chemotherapy followed by ASCT revealed that 11 (5.6%) of the 195 patients developed AT. The highest incidence of AT occurred during the induction course. A high incidence of AT was also reported in the above-mentioned large-scale study evaluating thrombosis in 18,637 patients with myeloma and 5326 patients with MGUS. Hazard ratios of AT at 1, 5, and 10 years after multiple myeloma diagnosis were 1.9, 1.5, and 1.5, respectively, and those at 1, 5, and 10 years after MGUS diagnosis were 1.7, 1.3, and 1.3, respectively (Table 3). These studies demonstrated increased incidence of VTE and AT in patients with myeloma compared to those without myeloma. The mechanisms of thrombosis in myeloma patients are multifactorial and include increased levels of procoagulant factors such as von Willebrand factor and factor VIII and high levels of inflammatory cytokines such as interleukin-6 and tumor necrosis factors.

**Conclusion**

Patients with lymphoma or myeloma are at increased risk for VTE, and perhaps for AT also. VTE tends to occur at diagnosis of cancer, early in the course of treatment for cancer, or during IMid-based therapy. The efficacy of prophylactic anticoagulants has been studied in solid cancer patients, but it is not currently well established. Some patients with lymphoma or myeloma have hemorrhagic tendencies, and anti-cancer agents used in patients with these diseases may cause severe thrombocytopenia; therefore, prophylaxis or treatment of thrombosis in these patients is more complicated than that in solid cancer patients. Our current understanding of the use of prophylactic anticoagulants is limited, and further research is needed to determine the optimal approach for prophylaxis in patients with lymphoma or myeloma. Further studies are also needed to elucidate the mechanisms underlying the thrombogenic effects of IMid-based regimens, particularly in Asian populations, in order to develop more effective and personalized thromboprophylaxis strategies.
lactic anticoagulants in patients with lymphoma or myeloma is shown in Table 4. Further studies are needed to develop a predictive model for identifying patients with lymphoma and myeloma who are at high risk for developing thrombosis and to evaluate adequate prophylaxis in these patients.

**Acknowledgment**

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