Coagulation in Cancer
Preface

During the past few years there has been considerable progress in elucidating the effect of cancer on the hemostatic mechanism. In a series of updated reviews, the contributors to this book describe the effects of cancer on coagulation and coagulation on cancer. In the first chapter, Monroe and Hoffman present their current concept of hemostasis, with an emphasis on the cell-based mechanism they recently delineated [1]. The authors describe how this system is perturbed by tumors. Next, Green and Karpatkin describe how platelets and thrombin interact with malignant cells, enhancing tumor cell adhesion and metastasis. In addition to activating platelets, thrombin activates several clotting factors, including factor XIII. Cancer promotes thrombosis by dysregulating tissue factor, cyclooxygenase, and plasminogen activator inhibitor-1, as discussed by Rickles and Falanga. In addition, procoagulants are active in oncogenesis and tumor metastasis. For example, fibrinogen produced by cancer cells promotes the growth of lung and prostate cancer cells through interaction with fibroblast growth factor-2 [2]. Activated FXIII supports the early survival of micrometastases in a mouse model [3]. Components of the plasminogen-plasmin system also play an important role in tumor growth, invasion, and metastasis as described by Kwaan and McMahon. In addition, cancer associated changes in this system increase the risk of bleeding and thrombotic complications. In the final chapter in this section, Sidhu and Soff explain how cancer-induced activation of coagulation promotes angiogenesis which enhances tumor cell proliferation, and how this phenomenon may be manipulated to curb tumor growth.

In the next section, Matzdorff and Green provide an overview of cancer-associated thrombosis, beginning with an historical note on Armand Trousseau, who emphasized the association between malignancy and thrombosis [4]. Ashrani and Heit review risk factors for thrombosis in cancer patients, noting that the risk varies by tumor type, stage of disease, and a number of patient-specific factors including inherited thrombophilia. For example, approximately 3% of lung cancer patients will develop venous thromboembolism within 2 years [5], and cancer patients with factor V Leiden have a 12.1-fold increased risk of thrombosis as compared to those without this mutation (5.1-fold) [6]. Specific thrombotic disorders associated with malignancy are tumor-associated microangiopathy, disseminated
intravascular coagulation (DIC), and migratory thrombophlebitis. Zakarija discusses thrombotic microangiopathies, their clinical manifestations and management. Saba, Morelli, and Saba review DIC. They note that the interplay of many mediators from the circulation, the cancer cells, and the host cells may be responsible for a particular thrombotic manifestation. The authors emphasize that control of the tumor is of primary importance, but there are other approaches that may be helpful in limiting the coagulopathy. In the next chapter, Tefferi reports that major thromboses at the time of diagnosis are found in 9.7–29.4% of patients with essential thrombocythemia, and in 34–38.6% of patients with polycythemia vera. He discusses the current management and risk stratification in these disorders as well as in primary myelofibrosis.

Iatrogenic thromboses in cancer patients may be due to chemotherapy and intravenous catheters. These risks are intensified by patient characteristics such as the site of the cancer, marked obesity (body mass index >35 kg/m²), anemia, thrombocytosis, or leukocytosis [7]. Ashrani and Rajkumar review the chemotherapeutic agents most commonly associated with thrombosis, and outline measures to prevent thrombotic complications when using these drugs. The topic of catheter-related thromboses is addressed by Freytes, who notes that there has been a recent decline in the frequency of this complication. Anticoagulant prophylaxis is probably not warranted for most patients needing central venous catheters, but when catheter-related thrombosis does occur, the use of antithrombotic agents is warranted. Allen and Bhat address thrombotic problems in children with cancer, and describe the diagnosis and management options specific to this population. Next, Lee discusses the management of venous thrombosis in cancer patients. The choice of anticoagulant, and the dose and duration of therapy, are described.
The treatment of the cancer patient presents certain challenges not present in patients without malignancies. These include the risk of bleeding due to chemotherapy-induced thrombocytopenia, recurrent and refractory venous thromboembolism, and concerns about maintaining the quality of life of patients with advanced disease. In the final chapter of this section, there is an examination of the effects of anticoagulants on cancer. The pioneering work of Zacharski [8, 9] suggested that the administration of warfarin to patients with small cell carcinoma of the lung resulted in a longer time to disease progression \( (p = 0.016) \) and improved overall survival \( (p = 0.018) \). We reported lower mortality in cancer patients treated with low molecular weight heparin as compared with standard heparin, and this was not due to a difference in deaths from thrombosis or bleeding [10]. Pineo and Hull review the literature regarding the beneficial effects of heparins on cancer survival and the effects of these anticoagulants on experimental models of tumor growth and metastasis. They illustrate the many pathways in hemostasis and angiogenesis that may be influenced by heparins and related compounds.

The final section of the book discusses bleeding problems in cancer, beginning with a review of cancer-associated thrombocytopenia by Eklund. A diagnostic algorithm for assessing thrombocytopenia in the cancer patient is presented, and the use of platelet transfusions for patients with decreased platelet production, as proposed by the American Society of Clinical Oncology [11], is discussed. Next, Zangari, Elice, Tricot, and Fink describe bleeding disorders associated with dysproteinemias. Bleeding is most frequent in patients with amyloidosis or Waldenstrom’s macroglobulinemia, but hemorrhage due to many other types of circulating clotting inhibitors has been described. In particular, acquired von Willebrand’s disease and specific inhibitors of factor VIII may be associated with recurrent and severe bleeding [12, 13]. The treatment of bleeding problems in cancer patients is addressed by Pereira. The use of topical agents, laser photocoagulation, and palliative embolization, as well as systemic therapy, is described, and the chapter concludes with a discussion of blood component usage.

This book is aimed at informing professionals working in the field of cancer about the pathophysiologic mechanisms of cancer-related thrombosis and bleeding. It will provide assistance in recognizing the various bleeding and clotting disorders associated with cancer. Further, it includes current recommendations for the management of hemorrhage, and prevention and treatment of thrombosis in the patient with malignancy. The editors anticipate that it will be a useful addition to the literature on cancer and coagulation.

References


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