Current Clinical Oncology
Series Editor: Maurie Markman

Amar Safdar *Editor*

Principles and Practice of Cancer Infectious Diseases

Humana Press

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Current Clinical Oncology

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ISBN 978-1-60761-643-6 e-ISBN 978-1-60761-644-3
DOI 10.1007/978-1-60761-644-3
Springer New York Dordrecht Heidelberg London

Library of Congress Control Number: 2011928679

Printed on acid-free paper

Humana Press is part of Springer Science+Business Media (www.springer.com)

This book is dedicated for promoting excellence in care and well-being for the patients with cancer.

Preface

Patients with cancer are highly susceptible to infections. These infections are inclined to be difficult to prevent, diagnose, and treat. There are a variety of reasons for this which will be discussed in detail in the chapters of this book. The intent for this book is to provide a comprehensive review of the ever changing spectrum of the management of infectious diseases in this complex population of patients. The changes in patient demography, near-constant global migration of contagious infections, emerging resistance to standard antimicrobial therapy, and the impact of expanding repertoire of antineoplastic therapies including the anticancer biologics and stem cell transplantation have influenced these changes. This book will provide a detailed guide for assessment of risk factors for various infections, evaluating prognosis among susceptible oncology patients with complex issues related to management of opportunistic infections. Strategies to promote hosts' immune response underscore the future measures based on perspicacious insight in the disease pathogenesis; interaction between the pathogen and host's immune function and inflammatory response are given prominent discussion throughout the book. I hope the reader will become acquainted with common and less often encountered infections and importantly, develop a keen knowledge of conditions that might be mistaken as infectious diseases in patients undergoing treatment for neoplastic diseases.

Houston, TX, USA — Amar Safdar, MD

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Part I
Overview and Special Population

Chapter 1
Infections in Patients with Cancer: Overview

Amar Safdar, Gerald Bodey, and Donald Armstrong

Abstract Patients with neoplastic disease are often highly susceptible to severe infections. The following factors influence the types, severity, and response to therapy of these infections: (1) Changing epidemiology of infections; (2) cancer- and/or treatment-associated neutropenia; (3) acquired immune deficiency states such as cellular immune defect; (4) recent development of new-generation diagnostic tools including widely available DNA amplification tests; (5) effective intervention for infection prevention; (6) empiric or presumptive therapy during high-risk periods; (7) availability of new classes of highly active antimicrobial drugs; (8) strategies to promote hosts' immune response; and (9) future measures. This introductory chapter intended for the reader to become familiar with the important historical milestones in the understanding and development in the field of infectious diseases in immunosuppressed patients with an underlying neoplasms and patients undergoing hematopoietic stem cell transplantation.

Keywords Cancer • Infection • Neutropenia • Immune defects • Diagnosis • Therapy

Patients with neoplastic disease are often highly susceptible to severe infections. These are inclined to be difficult to prevent, diagnose, and treat. There are a variety of reasons for this which will be discussed in detail in the chapters of this book. We will introduce this volume by reviewing the history and background of such infections, where we believe major advances have been made and what we believe will be necessary to effectively prevent and manage such infections in the future. The following factors influence the types, severity, and response to therapy of these infections: (1) Changing epidemiology of infections; (2) cancer- and/or treatment-associated neutropenia; (3) acquired immune deficiency states such as cellular immune defect; (4) recent development of new-generation diagnostic tools including widely available DNA amplification tests; (5) effective intervention for infection prevention; (6) empiric or presumptive therapy during high-risk periods; (7) availability of new classes of highly active antimicrobial drugs; (8) strategies to promote hosts' immune response; and (9) future measures.

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Historical Perspective

The introduction of chemotherapeutic regimens has expanded the population at risk, since many of these agents affect host defenses, most often causing neutropenia. However, even in acute leukemia, the malignancy with the highest frequency of infection, very little was published about infectious complications until the second half of the twentieth century. The paucity of published data is illustrated by a book on acute leukemia, published in 1958, which made no mention of infectious complications [1]. Indeed, at that time, some physicians attributed fevers in leukemia patients to a general hypermetabolic condition caused by the neoplasm.

By the 1950s, several antineoplastic agents became available which caused at least transient improvement in some malignant diseases. Nitrogen mustard caused responses in Hodgkin disease, aminopterin caused responses in acute leukemia, and methotrexate cured choriocarcinoma in women. The subsequent use of multiple drug combinations in acute lymphocytic leukemia and Hodgkin disease represented major advances [2]. Another important advance was the use of platelet transfusions to control and prevent hemorrhage in acute leukemia patients with thrombocytopenia [3]. In an autopsy study, the frequency of hemorrhage as a cause of death in acute leukemia patients decreased from 67 to 37% due to the use of platelet transfusions [4]. Unfortunately, infection remained a major cause of death. There have been many reviews of the subjects over the years, some with international contributors and continuity which are references here [5–11].

A. Safdar (ed.), *Principles and Practice of Cancer Infectious Diseases*, Current Clinical Oncology,
DOI 10.1007/978-1-60761-644-3_1, © Springer Science+Business Media, LLC 2011

Epidemiological Factors

Exposures to organisms in the distant as well as recent past should be considered in patients with neoplastic disease. Latent infections may be activated in the presence of waning immunity whether it be due to the disease itself or to the treatment. The classic example of this is reactivation of latent tuberculous in patients with treatment-induced helper T-cell dysfunction. Additional latent infections which may be activated, for example, are histoplasmosis, coccidiomycosis, disease caused by the Herpes group of viruses, toxoplasmosis, strongyloidiasis, and others. These demand consideration and many such as TB, herpes simplex, and strongyloidiasis can be effectively treated prophylactically. Recent travel or residence and hospitalization may expose patients to organisms which may incubate such as malaria after travel to an endemic area or colonization due to drug-resistant bacteria such as *Klebsiella*, *Pseudomonas,* and *Stenotrophomonas* species acquired during a previous hospitalization. Questions to investigate epidemiologic factors should include exposures at home along with work, habits, and hobbies. Also, a detailed history of recent and remote travel and recreational activities may provide clues for an otherwise improbable diagnosis. All of these can be a source of infection, some of which can be avoided with appropriate patient education.

Hosts' Susceptibility

It is not surprising that the frequency of infection is related to the type of underlying malignancy and most infections occur in patients who are failing to respond to their cancer therapy. Surveys in the 1960s found that about 80% of patients with acute leukemia, 75% with lymphoma, but less than 40% of patients with metastatic carcinoma developed infection [12, 13]. There are a wide variety of factors that may impact on the susceptibility of cancer patients to infection [11]. Local factors such as tumor masses that may obstruct the bronchial tree or urinary tract and necrotic tumors in the gastrointestinal tract can result in infection. In an autopsy study of children with metastatic carcinoma, 80% of cases of pneumonia were associated with pulmonary metastases, aspiration, or tracheostomy [14]. Antibiotic therapy is often of limited efficacy in these types of tumors, unless the local predisposing factor can be removed.

Immunological Factors

Neutropenia is the most important predisposing factor and can be due to the disease or its therapy. While there were some reports of the role of neutropenia in infection, a detailed analysis of 52 patients with acute leukemia was published in 1966 [15]. This study demonstrated that the risk of infection was related to the degree and duration of neutropenia. The risk increased when the neutrophil count was less than 1,000/mm^3, but increased substantially when it was below 500/mm^3. Also, the risk of developing infection increased the longer the duration of neutropenia. One hundred percent of episodes of severe neutropenia (<100 PMN/mL) lasting 3 weeks or longer were accompanied by identifiable infection compared to 65% of episodes lasting one week. Neutropenia diminishes the likelihood of detecting characteristic manifestations of infection. One study compared physical findings of infection in a group of patients with severe neutropenia with a group with adequate neutrophil counts [16]. Only 8% of patients in the former group with pneumonia were able to produce purulent sputum compared to 84% in the latter group. Similarly, among patients with urinary tract infections, pyuria was found in 11 and 97%, respectively. In an autopsy study, it was demonstrated that many pulmonary infections were not detected on routine chest radiographs antemortem [17]. Likewise, among patients with gram-negative bacillary pneumonia, 85% of those with initially abnormal chest radiographs had >1,000 neutrophils/mL, whereas 81% with normal roentgenograms had <1,000 neutrophils/mL [18]. The lack of signs of infection in febrile neutropenic patients impairs the physician's ability to determine whether or not fever is due to infection. In one study of fever in neutropenic patients, physicians were required to conclude whether infection was present or not before instituting therapy [19]. The physician's initial diagnosis (infection or fever of unknown origin) was incorrect in 33% of the cases.

White blood cell (WBC) transfusions were initiated in an effort to improve the outcome of infections in severely neutropenic patients. Since it was difficult to collect sufficient neutrophils from normal donors, initially, patients with chronic myelogenous leukemia with high neutrophil counts were used as donors [20]. Later, the development of the continuous cell separating machine made it possible to collect adequate cells from normal donors [21]. Studies demonstrated that there was a direct relationship between the number of cells transfused and the increment in the recipient's neutrophil count. In one study of 128 neutropenic patients who had fever unresponsive to antibiotic therapy, 49% responded after WBC transfusions, including patients with pneumonia and gram-negative bacillary septicemia [22]. Unfortunately, potential adverse effects occurred in some recipients. In one study when WBC transfusions were administered with amphotericin B, 64% of patients developed acute dyspnea, respiratory deterioration, and new pulmonary infiltrates compared to only 6% of patients who did not receive amphotericin B [23]. Several other studies failed to observe this toxicity. Another potential adverse event primarily for bone marrow transplant recipients was