Chapter 14
Infectious Diseases in Cancer Patients: An Overview

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Abstract The predisposition of cancer patients to infectious diseases which contribute to the gravity of their prognosis is well documented. The current success in therapy of both malignancies and infections is unprecedented. However, the overall co-morbidity of these conditions is still a major problem in management of these patients. Paradoxically, to some degree the problem of containing infectious complications is directly associated with the vigor of the anti-cancer therapeutic regimens. The objective of this chapter is to provide an up to date overview of our understanding of the infectious complications in cancer patients based on the type of infection and immune responses.

Keywords Cancer • Infection • Tumor immunology

Abbreviations

HBV	Hepatitis B virus
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
HAART	Highly active antiretroviral therapy
AIDS	Acquired immune deficiency syndrome
Treg	T regulatory cell
DC	Dendritic cell
IL-10	Interleukin 10
TGF-β	Transforming growth factor-β
MSC	Mesenchymal stem cell

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Introduction

The recently published book *Infectious Complications in Cancer Patients* by Valentina Stosor and Teresa Zembower offers an extensive coverage on this topic (Stosor and Zembower 2014). The objective of this chapter is to provide an overview of the most current status of this subject and to outline the major aspects of infectious diseases as one of the major causes of morbidity and mortality in cancer patients with emphasis on the latest publications in the field.

The spectrum of the infectious agents and clinical manifestations of the diseases, as well as the range of the diagnostic markers and technologies for their detection, are evolving features in the never ending battle against genetically non-self malignant and infectious invaders. This conflict is due to development of new infection- and cancer-defense mechanisms on one hand and the rapid progress of therapeutic interventions on the other.

The oncogenesis and development of the infectious diseases are both ultimately rooted in the compromised ability of the immune system to defend against non-self, either malignant or infectious, components. The underlying mechanisms of these two groups of disorders are complex and often interconnected. In some instances this pattern turns into a vicious circle. This is demonstrated in the cancers with viral etiology. Patients with HPV related squamous cell carcinoma, or HIV associated Kaposi sarcoma or HCV-induced hepatocellular carcinoma eventually become prone to viral, fungal, bacterial and other infections.

Genesis of the infectious complications in the cancer patients is based on local tumor-induced effects and on the mechanisms of generalized immunosuppression induced by both cancer-related processes and by the iatrogenic outcomes of the therapeutic regimens (Sutton 2014). The specific characteristics of the course and outcomes of the infectious diseases in cancer patients are defined by numerous factors, and are discussed in this chapter based on the type of infection and the immune system components involved.

Bacterial Infections

Bacteria represent the most common pathogen in cancer-associated infections, and bacterial sepsis continues to be a leading cause of morbidity and toxic death in children receiving intensive therapy for cancer (Alexander et al. 2012). It is well acknowledged that oncologic patients are more susceptible to bacterial infections and their systemic spread due to tumor-related and iatrogenic immunosuppression, which are comprised of the classic clinical combination of severe neutropenia, fever, hypotension and headache (Rasool Hassan et al. 2010). Acute bacterial infections negatively impact survival and increase mortality in adult and pediatric patients with solid cancers and hematologic malignancy (Lanoix et al. 2011; Attie et al. 2014; de Oliveira et al. 2014).

Further elucidation of the specific mechanisms and markers of the oncogenesis and cancer-associated infections allows development of target specific therapies. For example, it has been recognized that helicobacter pylori is one of the major causes of gastric cancer. The recently identified gastric stem/progenitor cell markers Lgr5, Villin-promoter, TFF2-mRNA and Mist and the gastric cancer stem cell markers such as CD44, CD90, CD133, Musashi-1 reveal novel information on tumor cell behavior and disease progression implicated for therapeutics (Ding and Zheng 2012).

New insight is currently emerging concerning the complexity of the infection-cancer-infection mechanisms interplay. The two major concepts being (i) the oncogenic role of the inflammatory cytokines and (ii) chemokine axis-based induction of the metastasis niches. It has been recently reported that systemic inflammation triggered by gastrointestinal tract bacteria plays a pivotal role in oncogenesis in the prostate gland (Poutahidis et al. 2013). Other recent research confirming the concept that inflammation is a critical component of tumor progression came from the study addressing correlation between oral bacterial infections and cancer. Inflammation caused by periodontal infections has been linked to cancer of the lung, kidney, pancreas, and hematologic and oral cancers (Pendyala et al. 2013).

The concept that metastatic spread of cancer can be promoted by bacterial infections was proposed based on studies on the CXCR4/ubiquitin axis. It was demonstrated that acute bacterial infections commonly seen in patients with cancer are linked to increased metastasis to the lung (Smith and Kang 2013). A model of the bacteria-induced acute lung inflammation was used to study its effect on lung metastasis in mice. Acute lung infection dramatically increased cancer cell homing to the lung and lung metastasis. It was also confirmed that the ubiquitin-CXCR4 axis plays an important role in these changes that were described as "preparation of a favorable metastatic niche" (Yan et al. 2013).

Allogeneic stem cell transplantation is a part of therapeutic modules in numerous cancers. Previous studies demonstrated that approximately 15–30 % of allogeneic hematopoietic stem cell transplantation recipients develop Clostridium difficile infection during transplantation, greatly exceeding rates in most other patient populations (Alonso and Kamboj 2014; Kinnebrew et al. 2014).

Fungal Infections

Fungi are the second most common pathogens after bacteria for causing cancer-associated infections in adult and pediatric patients with both solid organ- and hematologic malignancies. All organs from most commonly lung (Kim et al. 2014) to less frequently but associated with high mortality rates in pediatric cancer patients the central nervous system (Carter et al. 2015), are affected. Almost 50 % of the adult patients with acute myeloid leukemia that are subjected to chemotherapy develop invasive fungal infections (Neofytos et al. 2013). In pediatric oncology invasive fungal infections are also a frequent and potentially fatal complication

(Mor et al. 2011). Although solid tumors comprise the vast majority of cancers the morbidity and mortality due to fungal infections is higher in patients with hematologic malignancies. Invasive Aspergillus infection is one of the most common fungal infections that have been observed in patients with hematologic malignancy or those subjected to allogeneic hematopoietic stem cell transplantation (de Naurois et al. 2010). About 70 % of the pediatric oncology patients developing fungal infections have myeloid leukemia and acute lymphoblastic leukemia as their primary diagnosis (Mor et al. 2011).

The prolonged neutropenia of either primary or secondary genesis due to intensive chemotherapy regimens is the major predisposing factor for invasive fungal infections (de Naurois et al. 2010; Mousset et al. 2014). In addition, the fungal infection can develop as a complication of protracted use of venous catheters (Lai et al. 2004).

Aspergillosis is reported to have the highest incidence with Candidiasis second (Neofytos et al. 2013; Mor et al. 2011; de Naurois et al. 2010) and other fungal types of infections occurring less frequently as complications in adult and pediatric cancer patients (Kim et al. 2014; Caselli et al. 2014).

The increased intensity of chemotherapeutic regimens and rising resistance of fungal infections to antifungal drugs has prompted the search for new optimal prophylactic and therapeutic approaches. Antifungal drugs are often given prophylactically to patients with persistent fever, and are shown to decrease mortality rates (Johansen and Gotzsche 2014). Trimethoprim/sulfamethoxazole prophylactically administered before chemotherapy regimens has been shown to be effective in prevention of Pneumocystis pneumonia in children with solid tumors, leukemias and lymphomas (Caselli et al. 2014). However, caution in the choice of primary and secondary antifungal prophylaxis is recommended. The use of secondary prophylaxis may reduce systemic fungal infection frequency but at the same time increase the risk of colonization and infection with azole-resistant fungal strains (Gedik et al. 2014). Since it has been demonstrated that prolonged duration of neutropenia is one of the risk factors for onset of invasive Aspergillosis, addition of granulocyte-colony-stimulating factor into therapeutic and prophylactic protocols is recommended (van de Peppel et al. 2014).

Viral Infections

Viral infections are increasingly recognized as serious causes of morbidity and mortality in cancer patients. New technologies are emerging for their detection with respect to additional challenges in accurate and timely diagnosis and administration of appropriate antiviral therapy in this group of patients (Babady et al. 2012). Of special importance are the still open questions about interplay of the antiviral and anti-tumor immunity mechanisms, effectiveness and timing of vaccination and its relevance to chemotherapy regimens in the pediatric and adult oncology practice. Despite the significant advances in management of pediatric cancer and influenza,

the epidemiology and outcomes of influenza in pediatric oncology patients have not altered over the past several decades (Carr et al. 2012). Although influenza usually presents as a mild illness, children with hematological conditions and solid tumors are at increased risk for complications, which may lead to delay in anticancer therapy and increase in hospitalization and antibiotic usage (Ozdemir et al. 2011). Though influenza is the most common viral infection, is only one on the long list of viruses, such as H1N1, rhinovirus, parainfluenza virus, adenovirus, respiratory syncytial virus, human parechovirus, bocavirus, metapneumovirus, and human coronavirus occurring in about 30 % of neutropenic pediatric patients. Co-detection of these viruses is not uncommon, occurring in over 20 % of infections, in various combinations (Benites et al. 2014).

Cancer patients have unique problems associated with hepatitis B (HBV) and hepatitis C (HCV) virus infections. Of special concern is the risk of reactivation of infection due to viral replication as a result of immunosuppressive effects of the chemotherapy in general and of the new emerging modalities for targeted therapies. To date different outcomes in this respect of therapies using Alemtuzumab, Brentuximab, Imatinib, Cetuximab, Panitumumab, Ppilimumab were reported, and further randomized trials are needed to establish algorithms for this issue (Yazici et al. 2014). Also of consideration is the problem of balancing the chemotherapy and antiviral medication regimens and the timing of their administration. For some patients chemotherapy has to be postponed until completion of the antiviral course of therapy, while others cannot be subjected to the viral infection therapy while under treatment for their cancer (Borchardt and Torres 2014). One large study from Japan with evaluation of over 1,000 patients with breast cancer reported that chemotherapy for breast cancer patients with HCV infection is feasible, and according to their experience, viral load doesn't change during chemotherapy (Miura et al. 2013). Further elucidation is needed to clarify whether this outcome is cancer type or other factor-specific.

Cancer patients are at substantially increased risk of Herpes Zoster and related complications. The risk of Herpes Zoster infection in cancer patients compared to the general population is from 2 to 8-fold higher; with more than double the incidence in patients with hematologic malignancies as in those with solid tumors, including brain, lung, breast, esophageal, gastric and colorectal cancers (Hata et al. 2011; Habel et al. 2013). It has also been suggested that Herpes Zoster can be used as a marker for risk of malignancy, since there is a higher incidence of malignancy following an episode of Herpes Zoster in both men and women in all age groups 18 years and over (Iglar et al. 2013).

The mechanisms of HIV and oncogenesis are interconnected in adult and pediatric patients, and their co-morbidity is complex and multifactorial. Both, the HIV-associated immune activation and inflammation on one hand, and accelerated immune senescence on the other, favor cancer development. HIV-infected patients are at enhanced risk of several cancers, including lung and anal cancers, hepatocellular carcinoma, Hodgkin's lymphoma, Kaposi's sarcoma and several other cancers, compared to the general population (Sigel et al. 2011). Management of cancers in HIV patients is currently under intense research and is specific for each malignancy.

Highly active antiretroviral therapy (HAART) changed the course of HIVinfection. HAART reduced AIDS-defined-malignancies, but increased incidence of several non-AIDS-defined-malignancies (Chiappini et al. 2014). Adenocarcinoma of the lung is the most prevalent non-AIDS-defining cancer in the HAART era, and has up to four times greater incidence in HIV-infected individuals than in the general population. Two major problems are currently associated with management of lung cancer in HIV patents. Its diagnosis is often late because of onset in a younger population and its being clinically masked by or as a pulmonary infection, which are common among HIV-infected individuals. In addition, although there is increasing experience in using radiation and chemotherapy for HIV-infected patients who do not have surgical options, there is a need for more prospective studies because this population is frequently excluded from participating in cancer trials (Mani et al. 2012). This presents the necessity of including cancer screening in HIV-infected patients (Sigel et al. 2011).

Vaccination

All infections increase morbidity and mortality in cancer patients. Regimens for anti-infection therapy interfere with chemotherapy and other treatment modalities in this group of patients. In many cases this leads to the necessity of postponing the anti-tumor therapies to manage an infection, or vice versa, to delay the anti-infection medication until the chemotherapy is completed. In light of these negative impacts together with rising antibiotic resistance, development of preventive approaches to preclude the almost inevitable infectious complications, especially in neutropenic patients, is highly desirable. Need for infection prophylaxis is also growing in hematopoietic cell transplant recipients. Due to overall improvement of this treatment during the last two decades the survival duration has increased but the incidence of post-transplantation infections, particularly those caused by respiratory viruses, has concomitantly increased with lifespan. The lack of directed antiviral therapy for most viruses, has promoted the use of inactivated influenza vaccine for hematopoietic cell transplant recipients (Shah et al. 2012).

Reports on benefits and limitations of vaccination in cancer patients are numerous and contradictory. The overall trend is that influenza vaccination is beneficial in immunocompromised patients and significantly lowers the odds of influenza-like illness in patients with HIV infection, patients with cancer, and transplant recipients (Beck et al. 2012). A multicenter observational study has found that in cancer and hematopoietic stem cell transplant recipients with Influenza A (H1N1) the incidence of pneumonia was 66 % with an 18 % 30-day mortality, however no deaths were observed among vaccinated patients (Dignani et al. 2014). The study by Kim et al. addressed the immunogenicity of influenza vaccine in colorectal cancer patients based on antibody titers in blood samples. The data showed an acceptable immune response to an influenza vaccine without significant adverse effects, supporting the recommendation for annual influenza vaccination in colorectal cancer

patients (Kim et al. 2013). A simple prognostic measure was proposed for evaluation of the vaccination response to H1N1 virus. The study demonstrated that an absolute lymphocyte count above the lower normal limits for age prior to vaccination predicted the positive response to influenza vaccination in pediatric cancer patients treated with chemotherapy (Mavinkurve-Groothuis et al. 2013).

However, some caution was suggested in respect to the effectiveness of vaccination in cancer patients undergoing chemotherapy. The conclusion from the study by Shehata and colleagues was that although the active immunization in cancer patients has been shown to confer protective immunity against several infections at similar rates to healthy individuals, the immune responses to influenza vaccination in patients receiving chemotherapy were consistently weaker (Shehata and Karim 2014). Further clarification on optimal timing for vaccination in cancer patients is needed.

In addition, in one recent study the negative findings on the effectiveness of influenza vaccination in ovarian cancer patients were reported. The data in this study have shown that patients with ovarian cancer are almost uniformly unable to mount a meaningful antibody response to influenza vaccination and that despite CDC recommendations that patients undergoing chemotherapy receive influenza vaccine, there is little evidence to support its serologic effectiveness in these patients (Chu et al. 2013).

The Immune System and Cancer-Associated Infections

All components of innate and adaptive immunity are involved in shaping the course of malignancy, associated infectious diseases, and the ultimate prognosis for the patient. In addition to cellular immunity dysfunctions, these changes include alterations in cytokine profiles and humoral immunity reactions. Of special focus in this chapter are the latest updates from the rapidly evolving fields of study on the Dendritic and T regulatory cells, and neutropenia-related complications. Elucidation of the mechanisms of the immune system dysfunction on the type of cancer, nature of the infection and recently even individual patient levels allowed development of target specific therapies.

Dendritic cells (DCs) and T cells are among the major players sustaining physiologic immune conditions. Both are comprised of two functionally distinct populations: cells promoting immunity and those sustaining immune tolerance. Within T cells the functional subtypes can be easily identified as T effector and T regulatory (Treg) cells, respectively. Classification of different subgroups among dendritic cells is much more complicated. Originally DCs were discovered as cells of myeloid origin with mainly antigen-presenting function and thus as cells which promote mechanisms in adaptive immunity (Steinman 1991). Later it was recognized that depending on the DCs' maturation status (Steinman et al. 2003), hematopoietic lineage of origin (Ma et al. 2012) and expression of co-stimulatory and MHC molecules they can play either immunostimulatory or tolerogenic, immunosuppressive roles (Hurwitz and Watkins 2012; Zhong et al. 2014). In addition, the change from

immunostimulatory to tolerogenic status can be induced in DCs via different mechanisms by a number of malignancies. Also, it should be taken into consideration that over 60 % of malignancies arise in older populations, and hence the age-related decline in their hematopoietic cells' ability for self-renewal also contributes to an immunocompromised condition in cancer patients over 65 years old (Lipschitz 1995; Balducci et al. 2001; Shurin et al. 2007).

The ability of malignant cells to switch the DCs function from immunostimulatory into immunosuppressive cells is one of their essential immunomodulatory features. With the onset of malignancy complicated networks of expression in the ligand/receptor axis and changes in signal transduction lead to alteration of the functional profiles of the DC subpopulations. This has a twofold outcome. On one hand it is part of the tumors defense mechanism, protecting the malignant mass from immune reactions and allowing its unhindered growth. On the other hand, the tolerogenic function of the DCs leads to generalized immunosuppression, which contributes to the onset of infectious diseases. During the last decade new insights into particular mechanisms contributing to the tumor-induced changes in DC function and the resultant increased susceptibility to infectious diseases were reported. They include both local and systemic mechanisms employed by the tumor to affect the DCs functions. Collectively they result in the inhibition of the DCs differentiation from hematopoietic progenitors (Shurin et al. 2001; Tourkova et al. 2004; Hargadon 2013) and changes in their phenotype and function (Zhong et al. 2014; Aalamian-Matheis et al. 2007; Karthaus et al. 2012; Chao et al. 2015).

Dendritic cells often accumulate in and around tumors. However, their mere presence does not reflect their input in overall immunity and hence doesn't have prognostic value. They could either be part of robust anti-tumor immunity (Esche et al. 1998; Iida et al. 2008) or they may play an essential role in tumor immune escape (Zhong et al. 2014; Wu et al. 2014; Dudek et al. 2013). DC phenotyping is a valuable tool in defining their maturation and functional status. Multiple groups have reported data contributing to an optimal phenotyping panel of markers for tolerogenic/regulatory DC in cancer. It was shown that in prostate cancer expression of CD83, CD86 and CD40 co-stimulatory molecules are decreased (Aalamian-Matheis et al. 2007). It was also reported that evaluation of the tumor-infiltrating DCs should be performed utilizing a larger panel including not only S-100 and CD1a, but also DC-SIGN, and DC-LAMP markers (Karthaus et al. 2012). Detection of DC-SIGN is of importance because it is an intercellular adhesion molecule which can interact with carbohydrate structures on some cancer cells. This interaction leads to immunosuppressive responses in DCs via inhibition of their maturation (Chao et al. 2015). Also it was suggested that different levels of expression of the MHC and co-stimulatory molecules have representative patterns for different subsets of regulatory DCs (Zhong et al. 2014).

The major cancer-related factors triggering immunosuppressive DC function are Interleukin IL-10 (Shurin et al. 2002; Lindenberg et al. 2013; Kaebisch et al. 2014); TGF-β (Liu et al. 2012; Caux et al. 1999) and IL-17 (Wu et al. 2014). Recent insight into the mechanisms of a DC-related immunocompromised condition in cancer and cancer-associated infections has led to development of numerous therapeutic approaches utilizing DC-based vaccines (Mayordomo et al. 1995a, b; Tuting et al.

1997; Mayordomo et al. 1997; Burgdorf 2010; Cui et al. 2013; Duncan et al. 2013; Fadul et al. 2011; Niu et al. 2014; Ridolfi et al. 2010; Rosenblatt et al. 2013; Van Tendeloo et al. 2010; Suso et al. 2011) and other immunotherapies (Fang et al. 2014; Gao et al. 2014; Ghansah et al. 2013; Kobayashi et al. 2014; Lu et al. 2014; Wimmers et al. 2014; Yuan et al. 2014; Zhao et al. 2014).

T regulatory (Treg) cells play an essential role in negative regulation of the immune responses in both physiologic and diseased conditions. Evidence is mounting in support of their contribution to the processes of oncogenesis. A growing number of cancers have been shown to possess the ability to utilize different mechanisms attracting Treg cells and utilizing them in defense against immune reactions in an affected individual. The role of the Treg cells in enhancing the morbidity in cancer-associated infections is via local and generalized immunosuppression mechanisms. The trafficking patterns of the Treg cells can be altered by the tumor-secreted cytokines and chemokine molecules inducing their recruitment into the vicinity of the tumor and providing a malignant mass with 'a shield' that suppresses the anti-tumor immune responses. This allows for uninhibited tumor growth and also results in compromised anti-infection immunity. Among the list of this cohort of tumors are ovarian carcinoma (Curiel et al. 2004), breast tumors (Gobert et al. 2009), mesothelioma (Hegmans et al. 2006), Hodgkin lymphoma (Ishida et al. 2006), myelodysplastic syndromes (Kotsianidis et al. 2009), gastric cancers (Mizukami et al. 2008; Ohtani et al. 2009)., the malignant plural mesothelioma and effusions (Qin et al. 2009; Shimizu et al. 2009), and lung adenocarcinoma (Wald et al. 2006). CCL22, CCR4, CXCL9, CXCR4, CCR5, CXCL12 and CCL17 are among the chemokine molecules with altered expression which were reported to contribute to distorted trafficking patterns of Treg cells in cancer.

These findings triggered a new direction in the search for immunomodulatory therapies which target chemokine molecule expression in an attempt to rectify the Treg cells trafficking and function and to result in impeding tumor growth and ameliorating general immunosuppression and infection complications. The effectiveness of Treg cell depletion in the regression of oral fibrosarcoma with an increase in survival was demonstrated utilizing a mouse model. Anti-CD25 Ab administration resulted in depletion of the Tregs and a complete regression of tumor (Whelan et al. 2014). The following studies proposed further modifications in the use of anti-CD25 Abs. It was shown that targeting the CD25[Low] subset assures the discerning depletion of the Treg cells among other CD25+ T cell populations (Weiss et al. 2012). CD73 is a cell surface enzyme that suppresses immunity. The adoptive experiments in the Treg-deficient mice have demonstrated that protumorogenic effects of Treg cells depend on the expression of CD73. In vivo blockade of CD73 with a selective inhibitor or anti-CD73 mAb reduced tumor growth and metastasis (Stagg et al. 2011). Prostaglandin E2 (PGE2) and TGF-β play a role in induction of Treg cells. Interrupting the TGF-β and PGE2 signaling pathways was suggested as an alternative approach for reduction of the tumor protective function of Treg cells (Baratelli et al. 2010). Interest in adaptation of mesenchymal stem cell (MSC) transplantation for cancer therapy lead to the finding that migration of MSCs to the sites of tumor growth, which produced inhibition of Stat3 signaling, was associated with normalization of Treg numbers and dramatically reduced pulmonary and hepatic metastases

(Ling et al. 2010). Foxp3 is an X-linked nuclear transcription factor that is considered a defining marker for the Treg population (Sakaguchi 2004; Hori et al. 2003). Recently it was shown that Foxp3 not only plays a dominant role in the development and function of Treg cells, but also is a tumor suppressor factor (Heinze et al. 2011). This finding is of special interest since it was demonstrated that Foxp3-based tumor cytotoxicity is mediated via different signaling pathways compared to that enhancing the Treg cell function. This discrimination allows development of target-specific therapies aimed at augmentation of the Treg cells anti-tumor effects and not in altering their immunosuppressive function (Heinze et al. 2011).

Neutropenia. Neutrophils are among the cells acting as a first line of defense against infection mediated by innate immunity. Neutropenia, defined as an absolute neutrophil count below $1.5 \times 109/L$ (Newburger and Dale 2013), is a common complication in cancer. Neutropenia can develop as a result of malignancy affecting hematopoiesis directly, or via skewed production of growth factors and cytokines. In addition, neutropenia is a growing concern as a result of widespread use of aggressive chemotherapy (Nesher and Rolston 2013).

Several aspects of neutropenia are currently under thorough investigation in patients with cancer-associated infections. It was shown that in this group of patients neutropenia is associated with increased infection-related morbidity and mortality, and is directly correlated with the occurrence of sepsis (Cho et al. 2013). Cancer patients with febrile neutropenia episodes have a higher incidence of secondary infections. The presence of a central intravenous catheter, diarrhea and invasive Aspergillosis are among the predisposing risk factors (Azap et al. 2012). Cancer patients with febrile neutropenia which developed in association with hematologic neoplasms, who are undergoing high-dose chemotherapy regimens and develop bloodstream infection with Gram-negative multidrug-resistant bacteria, are reported to have prolonged hospital stays (Rosa and Goldani 2014).

In addition, determining the mechanisms underlying the onset of neutropenia are of interest in respect to discerning infectious versus sterile inflammation, which is frequently a challenge in cancer patients. A model to identify the infected from non-infected patients based on levels of a list of variables, which include acute phase proteins, cytokines, measures of coagulation, metabolism, organ stress and iron turnover was proposed for diagnostic evaluation in febrile neutropenic hematology patients (Wenneras et al. 2014). Evaluation of the risk of onset of neutropenia also plays a central role in development of the optimal prophylactic chemotherapeutic regimens and their duration (Weycker et al. 2014).

Conclusions

The susceptibility of cancer patients to various infections, with bacterial, fungal and viral being the most common, is due to both cancer-induced factors and iatrogenic outcomes of aggressive therapeutic regimens. The mechanisms evoking the immunocompromised condition in cancer of both origins and those contributing to higher

incidence and more aggressive course of infectious complications in this group of patients are complex and interconnected. The highest risk for onset of infectious complications and associated morbidity and mortality is seen in patients receiving chemotherapy for treatment of hematologic malignancies. A common occurrence for these patients is development of neutropenia, which is due to chemically induced suppression of hemopoiesis already compromised by malignancy. Ironically, in some cases the incidence of infections has concomitantly increased with a lifespan prolonged due to successful anti-cancer therapy. Thus, the ultimate goal of discerning the dichotomy of chemotherapy-mediated anti-cancer and immunosuppressive effects is of direct impact on management of infections in these patients. It is especially important in light of increased antibiotic resistance. New insight in the DC and Treg cell-mediated reactions leading to morbidity in cancer patients with infectious complications permits development of novel target-specific immunomodulatory therapeutic approaches.

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