**Considerations in the Application of Chemoprophylaxis Strategies in Immunocompromised Cancer Patients**

E.J. Bow MD, MSc., D. Bacteriol. FRCPC

Infectious Diseases, Haematology/Oncology, Blood and Marrow Transplant, Professor, Departments of Medical Microbiology and Infectious Diseases, and Internal Medicine, the University of Manitoba; Medical Director, Infection Control Services, CancerCare Manitoba, Winnipeg, Canada

**Introduction**

The numbers of patients who have disease- and treatment-related immunocompromising conditions leading to increased risk for life-threatening infection is increasing. The infections observed in these patients are often regarded as opportunistic, that is expression of clinical disease due to a wide spectrum of viruses, bacteria and fungi that would not cause disease in otherwise immunocompetent hosts. The broad principles of prevention of infections due to these organisms include prevention of exposure, prevention of expression of disease due to organisms colonizing integumental surfaces or to reactivation of those organisms lying latent in body tissues, and enhancement of host immune defence competence by reducing immunosuppressive influences. The domains in which chemoprophylaxis strategies have had the most impact is that of the quantitative suppression of certain enteric endogenous microorganisms that normally colonize neutropaenic patients’ intestinal mucosal surfaces and that of prevention of reactivation of certain DNA viruses lying latent in host cells and tissues.

The success of exposure prevention depends upon an understanding of the principles of airborne, aerosol, and contact transmission. Handwashing remains the most effective tool for limiting contact transmission. Employment of proper cough etiquette and, in some cases, use of face-masks may limit the projection of aerosols expectorated from infected patients. Protected environments have been useful in limiting airborne transmission of certain infections such as moulds.

**Anti-bacterial Prophylaxis in Neutropaenic Cancer Patients**

Severe neutropaenia secondary to cytotoxic therapy is associated with pyogenic infections due to gram-positive and gram-negative bacteria that are part of the normal microflora of the gastrointestinal tract. The use of fluoroquinolones has become a standard approach to the reduction in the risk for neutropaenic fevers, invasive infection due to aerobic gram-negative bacilli, and infection-related mortality. The intestine is the reservoir for these potential pathogens. Orally administered anti-bacterial agent can reliably eliminate susceptible enterobacteriaceae from the gut over the course of 7 days.

The prevalence of fluoroquinolone resistant (FQ-R) gram-negative bacilli is rising and threatens prophylaxis efficacy in patients with prolonged severe neutropaenia. There may be geographical limitations to the effectiveness of fluoroquinolone-based antibacterial prophylaxis in acute leukaemia patients. For example, FQ-R rates among *Escherichia coli* strains in northern Europe is less than 10%, whereas the rates may exceed 40% in southern European countries. FQ prophylaxis in the latter environment may not be as reliable as in the former for reducing the risk for invasive gram-negative infection. FQ resistance among
Enterobacteriaceae is linked to community FQ consumption that, in turn, encourages the transmission of multi-class anti-bacterial resistance genes among gram-negative bacilli.

Anti-bacterial prophylaxis is recommended for patients with expected durations of profound neutropenia (defined by an absolute neutrophil count of < 0.1 x 10^9/L) of ≥ 7 days, but not for those patients with solid tumours undergoing conventional cyclical chemotherapy with or without biologics such as cetuximab, rituximab, trastuzumab, or bevacizumab. The recommended duration of anti-bacterial prophylaxis extends from the initiation of cytotoxic therapy until myeloid reconstitution.

**Human Herpesviruses types I–V**

Prevention of reactivation of Human Herpesviruses types I, II, and III by the administration of nucleoside analogues has also become a standard of practice for sero-positive acute leukaemia patients undergoing remission-induction or post-remission consolidation chemotherapy and for haematopoietic stem cell recipients during the neutropaenic period prior to myeloid reconstitution or engraftment and during the first post-transplant month among solid organ transplant recipients. Longer term nucleoside-based prophylaxis over the first post-transplant year is recommended for the prevention of reactivation of Varicella-Zoster Virus (VZV) to cause cutaneous Herpes zoster (HZ, or “shingles”) and the syndrome of post-herpetic neuralgia (PHN). The impact of this strategy on the risk for HZ among haematopoietic stem cell transplant recipients has been a reduction from 25% to 7% for allografts and from 21% to 8% among autograft recipients. There is also a significant risk for HZ among solid organ transplant recipients; however, the incidence has ranged widely from 1.5% to 16.2% due to variations in the organs transplanted, immunosuppressive regimens employed, and deployment of anti-viral prophylaxis. In a cohort of 1,077 solid organ transplant recipients in the United States, HZ reactivation occurred in 90 (8.4%, 95%CI 6.8–10.2%). Of these patients, 23 (25.6%, 95%CI 17.7–35.4%) developed PHN. The reactivation rate appears highest for lung allograft recipients followed by heart, kidney, and liver. It is recommended that VZV sero-negative solid organ transplant candidates should receive live attenuated Oka strain varicella vaccine prior to transplant with two doses given 4–6 weeks apart and at least 2–4 weeks before transplant.

Recipients of the proteasome inhibitor, bortezomib, have a high risk for developing HZ. Experience has suggested that nucleoside analogues such as acyclovir or valacyclovir can reduce this risk significantly. Among 10 reports of treatment for myeloma or low-grade lymphomas from 2008 to 2013, Herpes zoster was reported in 34 of 1299 patients (2.6%, 95%CI 1.9–3.6%) not receiving bortezomib, 168 of 1640 bortezomib recipients (10.2%, 95%CI 8.9–11.8%), but in only 2 of 243 bortezomib recipients (0.8%, 95%CI 0.2–2.9%) given nucleoside analogue prophylaxis (χ² = 83.599, df = 2, P < 0.001).

Epstein-Barr virus (EBV), also termed Human Herpesvirus type IV, is a DNA virus that causes primary infections early in life often resulting in infectious mononucleosis in children and adolescents, chronic active EBV infection, and X-linked lymphoproliferative syndrome. EBV is also associated with a number of reactivation syndromes of latent infection including asymptomatic viraemia, encephalitis or myelitis, pneumonia, hepatitis, or a spectrum of EBV-associated malignancies including nasopharyngeal carcinoma, lymphoproliferative disease (LPD), Burkitt’s lymphoma/non-Hodgkin lymphoma (NHL), natural killer (NK)-cell leukemia, Hodgkin’s lymphoma, hemophagocytic lymphohistiocytosis, and angioblastic T-cell lymphoma. For stem cell transplant physicians, the most important sequelum of EBV reactivation is the post-transplant lymphoproliferative disorder (PTLD). The incidence of PTLD in EBV sero-positive stem cell transplant recipients varies by transplant type: 0.07% for allogeneic SCT, 0.45% for matched-related donor allografts, 1.4% for mismatched-related donor allografts, 4% for unrelated donor allografts, 4.5% for cord blood allografts, and 25% to 29% for haploidentical allografts and T-cell depleted matched unrelated donor allografts. Among solid organ transplant recipients, PTLD is observed in 1–2% of heart or liver allograft recipients, more than 5% of heart/lung recipients, and <1% among renal allograft recipients. For patients with haematological malignancies who are receiving conventional chemotherapy or autologous stem cell transplants for whom the risk of EBV PTLD...
is very low, no routine screening is recommended unless such patients are recipients of T-cell depleting therapies such as alemtuzumab or purine analogues. All allogeneic stem cell transplant recipients should be monitored for EBV reactivation. Anti-viral prophylaxis has no effect on the risk for PTLD and is not recommended for this purpose. With detection of EBV-DNAemia, a reduction in immunosuppression where possible and anti-CD20 therapy with rituximab are recommended to reduce the EBV-DNA load and progression to PTLD.\(^\text{28}\) The routine surveillance of adult transplant populations for EBV DNAemia by PCR has not been recommended outside the stem cell transplant population.\(^\text{30}\)

The risk for infection and clinical disease due to cytomegalovirus (CMV, human herpesvirus type V) is linked to patients’ serological status. Among CMV seropositive patients (or recipients of stem cell grafts from sero-positive donors) have a risk of CMV reactivation and expression of CMV disease of 45-86% and 20-30%, respectively.\(^\text{11,13}\) The risk of exposure of CMV to sero-negative patients undergoing treatments such as transplantation can be minimized by administration of CMV sero-negative or leukocyte-depleted blood products. All CMV sero-positive stem cell transplant recipients or sero-negative recipients of a graft from a CMV sero-positive donor should be placed on a CMV prevention strategy for the first 100 post-transplant days at least.\(^\text{13}\) Chemoprophylaxis with ganciclovir (GCV, 5mg/kg IV BID for 5-7 days then daily until day 100) to prevent CMV reactivation and replication has been recommended for allogeneic stem cell transplant recipients.\(^\text{13}\) Similarly, prophylaxis with GCV, acyclovir (ACV), or valacyclovir (ValACV) compared with placebo or no treatment has been effective in reducing CMV infection (RR 0.61, 95%CI 0.48-0.77), disease (RR 0.42, 95%CI 0.34-0.52), and all-cause mortality (RR 0.26, 95%CI 0.08-0.78) in solid organ transplant recipients.\(^\text{33}\) The administration of valganciclovir for up to 200 post-transplant days among donor-positive, recipient-negative recipients of renal allografts has been associated with a sustained reduction in CMV disease for up to two years.\(^\text{35}\) Preemptive therapy for CMV reactivation among high-risk transplant patients in whom evidence of CMV replication though serial blood sample monitoring for CMV antigen or DNA has also been shown to be as effective as prophylaxis for preventing CMV disease in solid organ\(^\text{36}\) and stem cell transplantation.\(^\text{13}\)

**Hepatitis B virus reactivation**

Approximately one-third of the world’s population has serological evidence of past or present infection with Hepatitis B virus. Three serologic tests (HBsAg, HBsAb, and HBcAb) have been advocated to distinguish those cancer patients at risk for primary infections or reactivation and who may be candidates for chemoprophylaxis.\(^\text{37}\) The detection of HBsAg identifies either a chronic HBV infection or a carrier state. Detection of HBV DNA in serum identifies the former. The combination of HBcAb positivity and HBsAg negativity identifies patients who are convalescent from a recent infection or those with an occult infection, the former with HBsAb positivity and the latter with HBsAb negativity (and detectable serum HBV DNA). Lamivudine reduces the risk for hepatic complications in cancer chemotherapy recipients with chronic HBV infections.

**Invasive Fungal Infections**

Invasive fungal infections (IFIs) caused by yeasts, such as *Candida* spp., and moulds, such as *Aspergillus* spp., may complicate the course of cancer patients receiving intensive cytotoxic therapy for acute leukaemia, those receiving T-cell suppressive therapy with purine analogues or alemtuzumab, and those undergoing allogeneic stem cell or solid organ transplant. Predisposing factors for invasive candidiasis (IC) include prolonged severe neutropenia, colonization of GI mucosal surfaces by *Candida* spp., and intestinal mucosal damage due to surgical trauma, graft-versus-host disease (GVHD), or cytotoxic therapy.\(^\text{38,39}\) The pathogenesis of IC involves translocation of *Candida* spp. colonizing the gut across damaged mucosal surfaces. Accordingly, orally administered anti-fungal agents such as the triazoles act by suppression of intestinal Candida colonization and subsequent infection.\(^\text{40}\) The risk of invasive mould infection in stem cell transplant recipients is a function of many factors including the underlying disease in the recipient, the human leucocyte antigen relatedness of the donor graft to the recipient, the source of the graft, and to the degree of the
associated immunosuppression. The pathogenesis of mould infections such as invasive aspergillosis (IA) involves the inhalation of air-borne conidia into the respiratory tract where they germinate into invasive hyphae. Triazole antifungal such as voriconazole or posaconazole may inhibit the germination process and limit invasion of tissues of the lung. The most common invasive fungal infections among solid organ transplant recipients include invasive candidiasis (IC, 59%), invasive aspergillosis (IA, 25%), invasive cryptococcosis (7%), invasive zygomycosis (2%), endemic fungal infection (2%), and other moulds (4%).

The American Society of Clinical Oncology recommends the use of an orally administered triazole antifungal or parenterally administered echinocandin in the outpatient setting as prophylaxis against opportunistic yeast infection in those with profound neutropenia and mucositis expected to last for > 7 days in environments with > 10% risk of invasive Candida infection; a mold-active triazole is recommended in environments with a substantial risk (> 6%) for invasive aspergillosis. Other guidelines groups have published similar recommendations. The duration of prophylaxis is linked to the infection to be prevented and to the presence of ongoing risk factors. For example, anti-Candida prophylaxis in acute leukaemia patients should extend from the initiation of induction therapy until myeloid reconstitution, whereas for allogeneic stem cell transplant recipients the duration extends from conditioning therapy until day 75-100 post-transplant.

Primary anti-mould prophylaxis may continue beyond day 100 for patients with active GvHD or ongoing immunosuppressive therapy. Among patients with a history of invasive fungal infection undergoing stem cell transplant, secondary prophylaxis is recommended to prevent relapse of the previous fungal infection.

Trimethoprim-sulfamethoxazole prophylaxis is effective for the reduction in the occurrence of pneumocystis pneumonia (PCP; RR 0.09, 95% CI, 0.02-0.32, NNT = 15) and PCP-related mortality (RR 0.17, 95%CI 0.03-0.94) and has been recommended where the event rate exceeds 3.5%. Such rates are observed among recipients of allogeneic stem cell transplants or solid organ transplants, acute lymphoblastic leukaemia patients, and those with severe combined immunodeficiency states. In addition, patients receiving fludarabine-based regimens such as fludarabine, cyclophosphamide, and rituximab (FCR) for indolent lymphoid malignancies have a PCP rate of 9% during therapy but double that (18.4%) during the year following completion of therapy. Accordingly, prophylaxis should be offered to such patients until 12 months post-FCR. Primary or metastatic brain tumour patients receiving doses of steroid (≥ 3 mg daily of dexamethasone equivalent) for ≥ 3 weeks are also at risk and should be offered prophylaxis. Prophylaxis should be administered for a month after the completion of corticosteroid therapy and recovery of the absolute lymphocyte count.

References


