Prophylaxis Against Fungal Infections and Cytomegalovirus Disease After Bone Marrow Transplantation

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Among the serious complications associated with bone marrow transplantation are invasive fungal infections caused by organisms such as Candida and Aspergillus species and end-organ disease caused by

the therapeutic modalities used to treat hematologic and solid-organ malignancies and to permit successful bone marrow or peripheral stem-cell transplantation dramatically increase the risk for infection in patients who are already immunocompromised because of their primary diagnosis. A myriad of possible infectious complications of bacterial, viral, fungal, or parasitic origin may develop as a result of immunosuppressive treatments. The risk for infection depends on the underlying disease process, previous infections, and most importantly, the degree and type of immunosuppression caused by the effects of pretransplant chemotherapeutic conditioning and posttransplant antirejection regimens on the immune system.

Neutrophil function, T-cell mediated immunity, humoral immunity, and intact integumentary and gastrointestinal systems are all altered to varying degrees by particular regimens. For example, disruption of cell-mediated immunity increases the risk for Pneumocystis carinii, tuberculosis and other mycobacterial diseases, Varicella zoster, Herpes simplex, and cytomegalovirus (CMV), while neutropenia predisposes a patient to bacterial and invasive fungal infections.[1]

Patients who are immunosuppressed as a result of bone marrow transplantation (or aggressive chemotherapy for leukemia or lymphoma) are at particular risk for these potentially devastating infections; effective, nontoxic prophylaxis would clearly be beneficial. Invasive fungal infections and end-organ disease caused by CMV are two of the most serious complications, leading to significant morbidity and mortality. Although there has been progress in the pharmacologic options available to prevent disease due to fungi and cytomegalovirus infections, the optimal approach to disease prevention that also minimizes the adverse effects of prophylaxis remains to be determined.

Prevention of Invasive Fungal Infections

Invasive fungal infections due to Candida, Aspergillus, and other pathogenic fungi are a significant problem, particularly in the setting of severe neutropenia. Candida species, usually Candida albicans, are the most common pathogens in this population. The risk of acquiring a severe candidal infection varies from one transplantation center to another. In a review of 1,506 bone marrow transplants performed over a 6-year period in Seattle, invasive infections developed in 11.4% of patients.[2] Fungemia was associated with a mortality rate of 40%, while patients with tissue-invasive disease had a mortality rate of 90%.

Predisposition to Infection

Candidiasis: The defects in host defenses that predispose a patient to candidal infections often occur in those undergoing cytotoxic chemotherapy for bone marrow transplant or neoplastic disease. To cause disease, Candida must first breach the defenses of the integumentary system, either through disrupted skin or gastrointestinal mucosa, and then disseminate through the bloodstream to organs such as the liver, spleen, and heart. Indwelling intravenous access devices, mucositis, and exposure to broad-spectrum antibiotics that suppress the normal bacterial flora and permit overgrowth of endogenous Candida are all risk factors for invasive fungal disease.[3] Defects in lymphocyte function and number predispose to mucocutaneous candidiasis, as typified by patients with human immunodeficiency virus (HIV) infection, but candidemia and deep-tissue infection are uncommon in HIV disease.
Neutropenia—particularly severe episodes below 500 cells per mm$^3$ that predictably occur with some cytotoxic chemotherapy regimens—increases the risk for invasive fungal infection. In a large series of bone marrow transplant patients followed by Goodrich and colleagues, risk factors for invasive candidiasis included older age, a diagnosis of acute myelogenous leukemia, mismatched allograft donor, acute graft-vs-host disease, and longer time to engraftment.[2] A study involving allogeneic bone marrow transplant recipients found high-dose corticosteroid therapy, prolonged neutropenia, and graft-vs-host disease to be significant risk factors.[4]

Aspergillosis: Aspergillus is the other common invasive fungus in immunocompromised patients. The rate of aspergillosis varies considerably from center to center and over time. This infection has been reported to occur in 5% to 24% of patients with acute leukemia and 0.5% to 9% of patients receiving bone marrow transplants.[5] Despite treatment, the mortality rate for invasive aspergillosis is at least 75%.[6]

Aspergillus is widely distributed in the environment. It has a predilection for the lung but can invade sinuses, brain, skin, and other organs. The primary risk factor for the development of aspergillosis is prolonged neutropenia, with a risk of 1% per day during the first 3 weeks of neutropenia, and 4% per day thereafter.[7] Other risk factors for aspergillosis that have been identified among bone marrow transplant recipients include older age, conditioning regimen, donor mismatch, and acute graft-vs-host disease.[6]

Prophylactic Antifungal Agents

Nonabsorbable antifungal agents such as nystatin or oral amphotericin B solution can treat and prevent oropharyngeal candidiasis and diminish the risk of colonization, but do not appear to prevent the development of invasive disease.[8] Intravenous amphotericin B produces significant toxicity, including nephrotoxicity. Ketoconazole (Nizoral) and intravenous miconazole (Monistat) are limited by drug interactions and other adverse effects.[8] The development of newer triazole antifungals—ie, fluconazole (Diflucan) and itraconazole (Sporanox)—and investigation of lower doses of amphotericin B have provided the best options for antifungal prophylaxis.

Fluconazole

Fluconazole has several advantages as a prophylactic agent, including its oral formulation, few adverse effects (primarily gastrointestinal upset and transaminase elevation), close to 100% bioavailability, and a long half-life that permits once daily dosing. It is active against Candida albicans and most other Candida species, with the notable exceptions of C glabrata, C krusei, and C parapsilosis. Fluconazole is not active against Aspergillus and other molds, and fluconazole-resistant strains of Candida albicans are increasingly common.

Fewer Fungal Infections: A randomized, double-blind, multicenter trial of fluconazole, 400 mg/d, vs placebo in neutropenic bone marrow transplant patients demonstrated a significant reduction in the incidence of systemic and superficial fungal infections.[9] Approximately half of 350 patients who received allogeneic transplants were given fluconazole or placebo until their neutrophil count rose to more than 1,000 cells per mm$^3$ or until they developed a (proven or suspected) fungal infection.

Invasive fungal infections developed in 15.8% of the placebo group, compared to 2.8% in the fluconazole group ($P < .001$). Although there was no difference in overall mortality at 90 days, significantly fewer deaths were attributable to fungal diseases in the treatment group than in the placebo group (1 vs 10, $P < .001$). The incidence of aspergillosis was low in both groups. Colonization and superficial fungal infections were also less common in the fluconazole group.[9]

Survival Benefit: Slavin and colleagues demonstrated a survival benefit with the use of prophylactic fluconazole from the onset of neutropenia to 75 days posttransplant.[10] In their study, 300 patients were randomized to fluconazole, 400 mg/d, or placebo and followed until either the development of systemic fungal infection or empiric amphotericin B use. Systemic fungal infection developed in 18% of patients in the placebo arm and 7% in the fluconazole arm ($P = .004$).
Fluconazole use also lowered the incidence of fungal colonization, superficial fungal infection, and empiric amphotericin B use. At 110 days, a survival advantage was noted for the fluconazole arm, with 31 deaths vs 52 deaths in the placebo arm ($P = .004$).

**Use in Hematologic Malignancies:** In a study population that included both bone marrow transplant recipients and patients with hematologic malignancies, a lower dose of fluconazole (200 mg/d) was examined for prevention of fungal infections during critical neutropenia.[11] Compared to the combination of clotrimazole, nystatin, and diphenhydramine, fluconazole was associated with both a lower incidence of systemic infection (7.1% vs 22.9%, $P < .05$) and death due to fungal infection (4.8% vs 18.8%, $P < .06$). The rate of colonization with *Candida* species was also lower with fluconazole.

Winston et al studied the use of prophylactic fluconazole in about 250 neutropenic patients undergoing chemotherapy for acute leukemia or blast crisis in chronic myelogenous leukemia.[12] Once again, fluconazole decreased the rate of both fungal colonization and the number of proven fungal infections (including superficial infections) from 21% to 9% ($P = .02$). However, a clear decrease in the incidence of invasive fungal infections, empiric use of amphotericin B, or mortality was not demonstrated.

A smaller trial of fluconazole in 151 neutropenic patients undergoing intensive chemotherapy with or without subsequent bone marrow transplant for acute myelogenous or lymphoblastic leukemia or high-grade lymphoma did not show a difference in mortality or in the number of invasive fungal infections. There were, however, fewer cases of oropharyngeal candidiasis and a longer time to empiric use of amphotericin B.[13] While no documented invasive candidal infections occurred in the fluconazole group, 8 of 75 patients developed mold infections, primarily *Aspergillus* species.[13] Despite controlling for both the type of underlying malignancy and the type of immunosuppressive therapy, the fluconazole recipients experienced a longer duration of severe neutropenia (less than 100 cells per mm$^3$). Fluconazole was not associated with this effect in the studies described previously.

A multicenter European trial compared fluconazole, 3 mg/kg, to oral nystatin, 50,000 U/kg, or amphotericin B oral suspension, 25 mg/kg, in 502 pediatric patients with hematologic and solid tumor malignancies. Although overall there were fewer fungal infections among those randomized to fluconazole, no difference was seen in the incidence of invasive disease among the arms.[14]

**Risks Associated With Prophylaxis:** Since fluconazole is not active against all species of *Candida* or against molds such as *Aspergillus*, there is a risk that prophylactic use will select for these organisms or increase the prevalence of resistant *C. albicans*. One center noted an increase in colonization by *C. krusei* and disseminated infection following widespread prophylactic use of fluconazole,[15] and later, an increase in fungemia due to *C. glabrata* among leukemic patients and those undergoing bone marrow transplantation.[16] It is notable that up to 46% of systemic candidal infections in oncology patients are due to species other than *C. albicans*.[17]

**Amphotericin B**

Amphotericin B is the gold standard for treatment of invasive fungal infections and for empiric antifungal therapy in neutropenic patients with persistent fever despite the use of broad-spectrum antibiotics. Adverse effects (particularly nephrotoxicity) and parenteral administration have limited its utility for prophylaxis. Oral amphotericin B has limited absorption, acting only within the oropharynx and gastrointestinal tract. It is no longer commercially available, although pharmacists can formulate a product intended for oral use from the intravenous product.

A randomized trial in Italy compared fluconazole, 150 mg/d, and oral amphotericin B solution, 500 mg administered every 6 hours, in 820 neutropenic patients with leukemia, and found the subsequent rate of invasive fungal infections in both groups to be less than 3%.[18]

**Low-Dose Intravenous Therapy and Risk of Toxicity:** The use of a lower dose of intravenous amphotericin B than that routinely used for treatment may minimize the risk of toxicity while providing protection against invasive fungal infections, including organisms such as *Aspergillus*. In a
comparison of fluconazole, 400 mg/d, and low-dose amphotericin B, 0.5 mg/kg 3 days a week, in 90 neutropenic patients with acute leukemia, 80% of those receiving fluconazole successfully completed the prophylaxis period, compared to 58% of amphotericin B recipients.[19] The rate of proven infections was less than 7% in both groups, although nephrotoxicity was more common in the amphotericin B arm.

However, in several studies using different dosing regimens, prophylactic intravenous amphotericin B showed no significant increase in renal toxicity in bone marrow transplant recipients. Riley and colleagues examined the use of low-dose amphotericin B, 0.1 mg/kg/d, in a small, randomized, placebo-controlled trial.[20] The incidence of systemic fungal infections was reduced, with no infections seen among the 17 patients in the amphotericin arm and five infections among the 18 patients receiving placebo ($P = .045$). A decrease in the duration of empiric amphotericin B use at standard dosage was noted in the amphotericin arm, as well as a trend toward improved survival and shorter hospital stay. However, this study was terminated early, without having accrued the planned number of participants, after Slavin et al reported a benefit for fluconazole over placebo.[10]

Perfect and colleagues investigated the use of low-dose amphotericin B in 182 autologous bone marrow transplant patients who were randomized to receive amphotericin B, 0.1 mg/kg/d, or placebo during neutropenia (mean duration: 14 to 16 days). [21] There was a decrease in oropharyngeal colonization but no statistically significant difference in empiric amphotericin B usage or in documented invasive mycoses. The low overall rate of fungal infection seen in this study[14.3% in patients randomized to placebo and 8.8% in those randomized to amphotericin B[21] compared to the studies described above may, in part, explain why no difference was demonstrated.

**Comparisons to Historical Controls:** Other studies are limited by comparison with historical controls rather than a randomized, concurrent placebo or active control group. Interpretation of these studies must be tempered by the fact that the rate of fungal infections, particularly aspergillosis, may vary over time due to factors such as changes in environmental contamination.

In the late 1980s, an uncontrolled trial of low-dose amphotericin B (5 to 10 mg/d) was conducted in allogeneic bone marrow transplant recipients who received the drug until hospital discharge.[4] In comparison to historical controls, the overall incidence of fungal infections in this trial decreased from 30% to 9%. The incidence of aspergillosis within the first 100 days decreased from 15.8% to 5.6%. Amphotericin B was not associated with increased nephrotoxicity, despite concomitant administration of multiple potential nephrotoxic agents.

In another center with a historically high incidence of aspergillosis, the use of prophylactic low-dose amphotericin B, 20 mg/d, plus nonabsorbable antifungal agents was initiated in 186 consecutive patients undergoing allogeneic bone marrow transplantation.[22] When compared to two historical cohorts, including one with strict environmental controls, there was a significant improvement in both confirmed aspergillosis and mortality; aspergillosis decreased from an incidence of approximately 24% to 9% by day 120, with no excess nephrotoxicity observed.

**Lipid Formulations:** With the advent of various lipid formulations of amphotericin B (Abelcet, Amphotec, AmBisome) and the lower incidence of dose-limiting nephrotoxicity, there has been renewed interest in prophylactic use of the drug. In one trial of liposomal amphotericin B (AmBisome), 76 patients undergoing bone marrow transplantation were randomized to a low dose (1 mg/kg/d) or placebo.[23] The active drug produced a decrease in the rate of fungal colonization but no difference in presumed or proven fungal infection. The only significant adverse effects were allergic reactions, which occurred in three patients.

Given the cost of the various liposomal preparations, the low toxicity rate reported with prophylactic doses of standard amphotericin B, and the limited data from randomized clinical trials, it would seem prudent to await the results of further trials before using liposomal formulations for this indication.

**Other Pharmacologic Options**

Other pharmacologic options available for prophylaxis include itraconazole and nasally administered amphotericin B.
Itraconazole: An oral azole derivative with good activity against *Aspergillus*, itraconazole requires gastric acidity for adequate absorption, thus limiting its usefulness in patients with impaired gastrointestinal function and mucositis. A prospective study of itraconazole for prophylaxis of fungal infections in neutropenic patients with acute leukemia found mortality from fungal disease decreased from 8.8% to 0.9%, compared to historical controls.[24]

A large trial comparing itraconazole solution, 2.5 mg/kg, to placebo in 405 patients receiving cytotoxic chemotherapy for hematologic malignancies or autologous bone marrow transplantation found fewer proven or suspected invasive fungal infections in the itraconazole arm (24% vs 33%, *P* = .035), with suspected fungal infection defined as persistent fever despite broad-spectrum antibiotics.[25] There was no significant difference in mortality or documented deep infection when considered independently.

Nasal Amphotericin B: Nasal administration of amphotericin B may exert a prophylactic effect against *Aspergillus* species during neutropenia by decreasing nasopharyngeal colonization. An Italian trial examined the use of a combination of itraconazole, 200 mg/d, plus nasal amphotericin B, 10 mg three times a day, in 164 patients with hematologic malignancies, neutropenia, and/or corticosteroid use.[26] In comparison to historical controls, the rate of proven aspergillosis dropped from 4% to 0%. There were no differences in the rates of invasive candidiasis (less than 3% in both groups) or in the use of intravenous amphotericin B.

Nasal amphotericin B alone, 10 mg daily in three doses, was examined in a small study of 34 neutropenic patients with malignancy.[27] Aspergillosis developed in two patients, a rate lower than that observed previously. Jeffery and colleagues performed a retrospective analysis of their experience in preventing aspergillosis during neutropenia with nasal amphotericin B, 7 mg aerolized in sterile water to each nostril four times a day.[28] In the 3 years following the introduction of nasal amphotericin B prophylaxis for all patients undergoing chemotherapy who were expected to experience prolonged neutropenia, no proven cases of invasive aspergillosis were seen, despite nearby construction and the documented presence of *Aspergillus* species by air sampling.

**Summary**

The evidence does not unequivocally support the use of antifungal prophylaxis for chemotherapy-induced neutropenia in patients with malignancies or bone marrow transplantation. The rate of invasive fungal infections due to *Candida* and *Aspergillus* species clearly varies over time and from center to center. Fluconazole, typically at doses of 200 to 400 mg/d, is useful in patients with prolonged neutropenia in settings where invasive candidiasis is common. In centers where aspergillosis is a problem, prophylaxis with low-dose intravenous amphotericin B may provide protection against *Aspergillus* as well. The optimal dose and schedule has not been established, but it appears that the risk of nephrotoxicity diminishes with low doses. The use of itraconazole or nasal amphotericin B may also have a role, but the available evidence is not conclusive.

**Cytomegalovirus Prophylaxis**

Cytomegalovirus is the other major infectious threat following bone marrow transplantation. At least 50% of the population has IgG antibody to CMV, indicating latent infection and therefore, with immunosuppression, a potential risk for CMV reactivation. Defects in cell-mediated immunity, such as the profound disruption caused by the immunosuppressive regimens required for successful engraftment, increase the risk for CMV end-organ disease. Patients with malignancies who receive immunosuppressive chemotherapy without undergoing bone marrow transplantation do not share the same degree of risk for CMV disease, perhaps due to a shorter or less severe degree of immunosuppression as well as diminished exposure to exogenous sources of infection.

Cytomegalovirus infection is usually defined as asymptomatic shedding of the virus and must be distinguished from invasive end-organ disease, which has specific clinical manifestations. Different immunosuppressed populations have distinctly patterns of invasive CMV disease. In bone marrow transplant recipients, CMV disease most commonly occurs as a progressive and potentially fatal...
pneumonitis, although it can affect almost any organ.

While CMV infection occurs in over 50% of bone marrow transplant patients, invasive disease develops in about 10% of allograft recipients and 2% of autograft recipients.[29] The primary risk factors for the development of CMV infection (in addition to allogeneic transplantation) are the serostatus of the recipient and the development of acute graft-vs-host disease.[30,31] Receiving marrow from an unrelated donor is an additional risk factor.[32] Patients with CMV antibodies, who receive marrow from a CMV negative donor, also appear to have an increased risk of CMV disease.[33] The seronegative patient receiving marrow from a seronegative donor can be protected effectively from de novo infection by administration of blood products from CMV negative donors.[34]

**Preventive Strategies**

Because mortality from CMV pneumonitis remains high despite antiviral treatment, there is much interest in preventive strategies. Targeting those patients at greatest risk for developing CMV disease would reduce unnecessary exposure to potentially toxic antiviral agents. The detection of CMV shed in urine or blood cultures is not always predictive of subsequent tissue-invasive disease. Moreover, invasive CMV disease can occur before the detection of viremia.[35] This has led to the development of more sensitive methods of detecting CMV before end-organ disease occurs. These include the detection of specific CMV antigens such as pp65 and detection of CMV DNA by polymerase chain reaction (PCR) technology. Each technique is associated with various advantages and disadvantages, but both have good sensitivity and specificity for active CMV replication that presages end-organ disease.[36,37]

A number of different strategies for approaching CMV infection in bone marrow transplant recipients have been explored. These include the prompt use of specific antiviral agents for treatment once clinical signs and symptoms have developed, prophylaxis (administration to all patients at risk), and preemptive treatment (initiating antiviral therapy when CMV is detected by culture, PCR, or antigenemia but before end-organ disease is apparent).[38]

**Agents for Preventing CMV Disease**

**Acyclovir**

Acyclovir, which is used for the prevention of other herpesviruses, has also been studied for the prevention of CMV. Although it is more active against *Herpes simplex* virus (HSV) and *Varicella zoster* virus (VZV), it does display some anti-CMV activity at high doses and has little hematologic toxicity.

Meyers et al administered intravenous acyclovir, 500 mg/m$^2$ every 8 hours, to patients who were seropositive for HSV and CMV from 5 days before to 30 days after undergoing allogeneic bone marrow transplantation. Compared to a control group comprised of patients who were CMV-seropositive only, the acyclovir recipients had fewer CMV infections by day 100 (59% vs 75%), a lower rate of invasive disease (22% vs 38%), and improved overall survival that was not strictly due to prevention of CMV alone.[39]

A multicenter trial in 310 allogeneic bone marrow transplant patients who were CMV seropositive or had seropositive donors examined the following three regimens of prophylactic acyclovir: intravenous delivery at a dose of 500 mg/m$^2$ every 8 hours from day -5 to day 30, with or without high-dose oral acyclovir (800 mg four times daily for the next 6 months), vs low-dose oral acyclovir, 200 to 400 mg four times daily for the first month.[40,41] By day 210, the rate of CMV infection was 61% in the low-dose group, compared with 52% in the group receiving intravenous followed by high-dose oral acyclovir ($P = .046$), and 49% in the group that received intravenous acyclovir only ($P = .024$). Because all study participants were eligible to receive preemptive treatment with ganciclovir at the physician’s discretion, interpretation of study outcomes is unfortunately compromised. The mortality rate at 1 year was 32% in the group receiving prolonged acyclovir prophylaxis, compared to 51% in the group receiving low-dose oral acyclovir ($P = .01$).
Ganciclovir

Ganciclovir, a derivative of acyclovir with significantly better activity against CMV, can be used for prophylaxis, although it can cause problematic neutropenia and, less commonly, thrombocytopenia.

Goodrich et al administered intravenous acyclovir to 64 allogeneic transplant recipients until engraftment, followed by either ganciclovir, 5 mg/kg twice daily for 5 days, then once a day until day 100, or placebo.[42] The rate of CMV infection fell from 45% in the placebo group to 3% in the ganciclovir group (P < .001), and the rate of CMV disease fell from 9% to 0 by day 100 (P < .001). Remarkably, there was no demonstrable survival benefit. Neutropenia occurred in one-third of the patients on ganciclovir and was associated with an increased risk of bacterial infection.

Winston et al investigated another ganciclovir regimen: CMV-seropositive patients undergoing allogeneic bone marrow transplant were randomized to placebo or intravenous ganciclovir administered at a dose of 2.5 mg/kg three times daily for the week before transplant, and then at 6 mg/kg/d, 5 days a week, once the neutrophil count reached 1,000 cells per mm. [43] Cytomegalovirus infection developed within the first 120 days posttransplant in 56% of the placebo recipients, compared to 20% of the ganciclovir recipients (P < .001). Less CMV end-organ disease was observed in the ganciclovir arm, although the difference was not statistically significant. Again, neutropenia was a significant adverse effect, occurring in almost 60% of those randomized to ganciclovir. However, the majority of patients were able to resume ganciclovir therapy after the neutropenia resolved.

Several smaller studies with historical controls have also demonstrated reductions in both CMV infection and disease with prophylactic ganciclovir. No CMV disease developed in 25 patients who received ganciclovir, 5 mg/kg twice daily for the week before transplantation, oral acyclovir until day 20, and then ganciclovir 5 mg/kg three times a week until day 84. This was compared to a historic rate of 23%.[44]

In another study of 40 patients who received ganciclovir, 6 mg/kg/d the week before transplant and then 6 mg/kg/d 5 days a week from day 30 to day 90, one developed CMV disease, compared to 59% of historical controls.[45]

An uncontrolled study of a lower dose of ganciclovir in 41 patients undergoing T-cell depleted allogeneic marrow transplantation did not demonstrate any protection against CMV infection or disease. Ganciclovir was administered at a dose of 2.5 mg/kg three times daily for the week prior to transplantation, and then at 6 mg/kg three times a week from engraftment to day 100. By day 120, 25% of the patients had died from CMV-related causes. Myelosuppression was common even at these lower doses, and 29% of patients developed bacteremia while neutropenic.[46]

**Targeting Ganciclovir Prophylaxis:** Although the administration of ganciclovir to all allogeneic transplant recipients who are CMV-seropositive or have a CMV-positive donor significantly diminishes the risk of developing CMV disease, it also exposes a significant proportion of patients to a myelosuppressive agent and the attendant risks of prolonged neutropenia. An alternative approach would be to initiate preemptive treatment with ganciclovir when surveillance cultures reveal active CMV replication.

Goodrich and colleagues screened a population of 287 allograft recipients who had CMV antibodies or a CMV-positive donor for evidence of CMV replication with weekly throat, blood, and urine cultures; a subgroup also underwent bronchoalveolar lavage.[47] All patients received high-dose intravenous acyclovir for the first 30 days posttransplantation. After a positive screening culture had been obtained, 72 patients were then randomized to receive ganciclovir, 5 mg/kg twice daily for 1 week and then once daily until day 100, or placebo.

Ganciclovir decreased the incidence of CMV disease from 43% to 3% (P < .00001), doubled the clearance of positive cultures, and improved overall survival by day 180 (P = .027). Neutropenia was more common in the patients receiving ganciclovir. One drawback of this approach is that 12% had already developed CMV disease by the time surveillance cultures became positive.
Performance of bronchoalveolar lavage at day 35 in all CMV-positive patients undergoing allogeneic transplantation or those who had a seropositive donor is a variation on this approach. In another study, patients with positive bronchoalveolar lavage cultures (n = 40) were randomized to receive ganciclovir, 5 mg/kg twice daily for 2 weeks and then once daily until day 120, or placebo.[48] The incidence of CMV pneumonitis was reduced from 70% to 25% among those randomized to ganciclovir (P = .01). Of the 55 patients whose bronchoalveolar lavage cultures were negative, 22% later developed pneumonitis—a significantly lower rate than that seen in the placebo group with positive bronchoalveolar lavage cultures (P = .003).

In an effort to target prophylactic treatment more efficiently, Boeckh and colleagues investigated the use of the CMV pp65 antigenemia assay to guide the preemptive use of ganciclovir. They randomized 226 CMV-seropositive patients undergoing allogeneic bone marrow transplant to prophylactic ganciclovir at engraftment or placebo.[49] If high-grade antigenemia was detected, open-label ganciclovir was administered at 5 mg/kg twice daily for 7 days and then once daily for a total of 3 weeks, or for 6 days after the resolution of antigenemia, whichever was longer. In the case of recurrent antigenemia, ganciclovir retreatment for 2 weeks was permitted. There was a higher incidence of CMV disease by day 100 in the antigen-based treatment group (14% vs 2.7%, P = .002). The ganciclovir arm had more invasive fungal infections and more late-onset CMV, making the overall survival rates equivalent.

A smaller study examined the use of PCR to direct preemptive treatment. Screening for CMV replication by culture or PCR was performed in 71 allogeneic transplant recipients.[50] Ganciclovir, 5 mg/kg twice daily for 2 weeks, was given to patients with a positive blood, urine, or throat culture as well as to those with two positive PCR tests. Daily ganciclovir was continued until PCR testing proved negative. The incidence of CMV disease by day 100, (23% vs 5%, P = .04), was significantly lower in the PCR-monitored group, as was CMV-related mortality (P = .02). No patient with a negative PCR test developed CMV disease. However, after day 100 and the cessation of PCR screening, nine patients in this group developed late CMV disease.

Foscarnet

Foscarnet (Foscavir), a pyrophosphate analog that, like ganciclovir, inhibits DNA polymerase, is active against herpesviruses including CMV. Ippoliti et al examined the use of foscarnet in patients undergoing allogeneic bone marrow transplantation, some of whom received T-cell depleted marrow.[51] Patients were eligible for foscarnet if they had delayed engraftment or ganciclovir-induced neutropenia. Cytomegalovirus infection or disease developed in 6 of 39 patients receiving intravenous foscarnet, 60 mg/kg once daily; adverse effects—nephrotoxicity, nausea, and vomiting—were mild.

However, smaller trials conducted previously found that foscarnet was less effective than ganciclovir, with a nephrotoxicity rate approaching 50%.[52-54] Lower doses and adequate hydration can prevent nephrotoxicity. Until foscarnet and ganciclovir are compared in a study with adequate power, foscarnet should only be considered for use in patients with prolonged neutropenia or in those with ganciclovir intolerance or resistance.

Summary

Although ganciclovir has proven useful after bone marrow transplantation, adverse effects can be treatment-limiting. Drug-induced neutropenia develops in up to 30% of patients, increasing the risk for serious bacterial and fungal infections, and 8% of those who discontinue ganciclovir for neutropenia subsequently develop CMV pneumonitis.[42,43] The use of hematopoietic growth factors such as granulocyte colony-stimulating factor (G-CSF [Neupogen]) may ameliorate neutropenia and enable ganciclovir to be continued.

Late-onset CMV disease has been noted after cessation of ganciclovir prophylaxis in up to 15% of bone marrow transplant patients.[42,47,49] The recovery of CMV-specific T-cell responses following bone marrow transplant is crucial for protection against CMV, and the use of prophylaxis appears to delay recovery of these responses.[55]
As more sensitive methods for identifying active CMV replication such as quantitative PCR are developed and our understanding of the processes involved in CMV reactivation disease increases, it may be possible to target CMV prophylaxis more effectively. This should minimize both unnecessary exposure to toxic agents and the number of patients who develop CMV disease before surveillance tests prove positive. Ultimately, increased insight into the immune response to infection and ways to restore CMV-specific immunity may decrease the need for antiviral prophylaxis.

**Conclusions**

Patients undergoing bone marrow transplantation or aggressive chemotherapy are at risk for invasive fungal infections. Allogeneic (and to a lesser degree, autologous) bone marrow transplantation increases the risk of developing CMV end-organ disease. Defining the degree of risk for a particular patient is useful for determining whether antifungal or anti-CMV prophylaxis should be employed. Although the available approaches are useful in selected patient populations, the risk of adverse drug effects and pressure toward resistance development must be considered.

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