Viral infections in neutropenia—current problems and chemotherapeutic control

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The risk of infection in immunocompromised patients is determined by the nature, degree and duration of the immunosuppressive disease or therapy. Although neutropenia is clearly related to an increased risk of infection, these infections are typically caused by bacteria and fungal pathogens rather than by viruses. Viral infections are predominantly associated with defects in cellular immune function and might not be expected to cause problems in patients whose primary disease is accompanied by neutropenia. The net state of the patient's host-defence mechanisms is, however, a complex interplay between a number of factors, primary among which are the underlying disease and the nature of the therapy being given. In certain periods of neutropenia, therefore, particularly that occurring early after bone marrow transplantation, viral infections are commonly seen. The viruses responsible are chiefly the herpesviruses, both primary infections and reactivation, although other viruses are assuming recognized importance in this setting. This article provides a review of the infections that are encountered during the period of neutropenia in immunocompromised patients and the options available for chemotherapeutic management.

Introduction

Neutropenia, however, usually results from the administration of chemotherapy or radiation therapy and this may be given for a disease with a primarily cellular defect. These patients may then present with disease due to their cellular defect but at a time of neutropenia induced by cytotoxic chemotherapy. A combination of neutropenia and defective cellular immune function, which will predispose to viral infections, is particularly likely to occur in groups of patients either with disease such as aplastic anaemia or those given cytotoxic therapy that is myelosuppressive. The latter groups include those with acute leukaemia or other malignancies, especially small-cell carcinoma of the lung, testicular carcinoma and some sarcomas, those with Hodgkin’s or non-Hodgkin’s lymphoma or human immunodeficiency virus (HIV) infection (who will have an inherent abnormality in cellular immune function) and those who have received a bone marrow transplant (BMT).

The period of profound myelosuppression induced by chemotherapy in patients with leukaemia or other malignancies is variable. In some instances, for example ‘consolidation’ chemotherapy or cis-platinum therapy of germ-cell tumours, the period of neutropenia is often quite short (only 7–10 days) but wider use of more intensive
chemotherapeutic regimens in haematological malignancies and solid tumours has led to somewhat longer periods of neutropenia. Bone marrow transplant recipients typically have neutropenia (<0.5 \times 10^9/L) during their initial ablation and conditioning period, from approximately 1 week before to 2–3 weeks after transplantation. There are, however, 10% or so of patients who have prolonged neutropenia, lasting for 2–3 months after transplantation. In many of these patients the defect in cellular immune function and hence the increased risk of intracellular and opportunistic pathogens, including viruses, will persist for considerably longer than the period of neutropenia. It has now become apparent that different viruses affect immunosuppressed patients, particularly organ transplant and BMT recipients, at different times in the period of immunosuppression (Figure).

Of these opportunistic viral infections, the ones that are likely to occur during a period of neutropenia are, in general, those that tend to present in the first month after remission induction or transplantation. Non-bacterial pathogens, among them viruses, either reactivated or freshly acquired, are also of importance during the longer periods of neutropenia that are seen in some BMT recipients.

The viral infections that are particularly common in patients with neutropenia are, therefore, primary infections with herpesviruses, respiratory viruses, adenoviruses and other gastrointestinal viruses, and reactivation of latent herpesviruses, particularly herpes simplex virus (HSV) and cytomegalovirus (CMV), especially in BMT recipients.

Although it is of vital importance in increasing the risks of infection, the immunomodulating effect (including the production of neutropenia) of many viral infections, particularly CMV, Epstein–Barr virus and the hepatitis B and C viruses, will not be discussed in any detail in this review since the consequences of this immunomodulation are an increase in the occurrence of non-viral opportunistic infections.

**Epidemiology**

Reactivation of latent HSV is the most common viral infection in patients during the profound neutropenia that occurs during remission induction in patients with lymphoma and acute leukaemia and during the conditioning phase of bone marrow transplantation (the first 2–3 weeks after transplantation)—indeed, HSV is the only common viral infection at this stage. Eighty percent of BMT patients who are seropositive for HSV but less than 1% of seronegative patients will have asymptomatic shedding of HSV in their saliva some time in the first 50 days following transplantation. The peak time for HSV excretion occurs 2–3 weeks after transplantation and in only 10% is excretion first detected >6 weeks after the transplant. Such HSV shedding is predictive of reactivation of HSV to cause herpes labialis and oropharyngeal disease.

The percentage of patients with leukaemia and other forms of immunocompromising disease who reactivate HSV is somewhat lower. Saral et al. studied HSV-seropositive patients with acute leukaemia who were undergoing induction therapy with cytarabine and daunorubicin: 25% of the group had virus detectable in their saliva. Similar results were obtained by Lam et al. amongst patients with acute myeloid leukaemia. The occurrence of HSV infection is correlated with the level of complement fixing antibody with more than 60% of those with titres of \( \geq 1:16 \) reactivating at a median time of 18 days after induction therapy.

**Clinical features**

HSV reactivation causes an increase in the severity of oral mucositis in profoundly immunocompromised patients (Table). Intraoral ulcers outside the gingival margin are rarely seen in normal healthy people but such ulcers occur in about 30% of neutropenic patients. The role of HSV in the aetiology of these ulcers has recently been clarified in a double-blind placebo-controlled trial of acyclovir in patients with acute myeloid leukaemia. The incidence of all acute oral infections (not just those that were HSV

| Table. | The relationship between salivary HSV excretion and the severity of oral mucositis in BMT patients (adapted from Walter & Bowden)
<table>
<thead>
<tr>
<th></th>
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<tbody>
<tr>
<td>Clinical severity of mucositis (grade)</td>
<td>0</td>
<td>1-2</td>
</tr>
<tr>
<td>Total no. of patients</td>
<td>22</td>
<td>44</td>
</tr>
<tr>
<td>No. excreting HSV</td>
<td>3 (14%)</td>
<td>15 (34%)</td>
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</tbody>
</table>

*Grade 0 representing no mucositis and grade 4 representing life-threatening mucositis.
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Prevention of reactivation. Several studies have shown that HSV after chemotherapy or BMT for haematological malignancy may be prevented by acyclovir prophylaxis given to those who are HSV-seropositive. Since the degree of seropositivity correlates with risk of disease, prophylaxis is generally only needed for those with higher levels of antibody ($\geq 1:16$).11,12 Either iv acyclovir 250 mg/m$^2$ bd or tds, or oral acyclovir (400 mg five times daily or 800 mg bd), starting 1 week before BMT or induction and continuing until 4 weeks afterwards, may be used.11,12 Such prophylaxis is about 90% effective in preventing HSV disease.13 Since it has a broad spectrum of activity against herpesviruses, the use of ganciclovir early following BMT to prevent CMV disease will also significantly reduce HSV excretion and disease.14 New antiviral compounds with activity against HSV have been introduced but, as yet, there are no studies of the use of famciclovir or valaciclovir (a prodrug of acyclovir) in immunocompromised patients.15

Management

HSV strains resistant to acyclovir have been isolated from 5–10% of BMT patients given acyclovir and sometimes these resistant strains can cause severe visceral infections.16 Most such strains are resistant as a result of a mutation in the gene encoding for thymidine kinase, leading to a relative deficiency or lack of thymidine kinase, the viral enzyme needed for the first step in the conversion of acyclovir to its active triphosphate form. These resistant strains are cross-resistant to ganciclovir, foscarnet and valaciclovir and the treatment of choice is foscarnet.20

Cytomegalovirus

Epidemiology

Human CMV is a common infection, with between 40% and 100% of adults seropositive in different geographic and socio-economic populations. In common with other herpesvirus infections, primary infection (which is often asymptomatic in the healthy host) is followed by latency. CMV latency is maintained in several tissues including mononuclear cells and salivary glands. Persistent viral excretion and recurrences often result from reactivation of the latent virus, although re-infection with another strain of CMV can sometimes occur, particularly in the immunocompromised individual. In the immunocompromised population, reactivations of genital HSV are less common than oropharyngeal infections but, when they do occur, they can be equally severe.

Other forms of clinical disease caused by HSV in leukaemia or after BMT include: oesophageal HSV, which is usually secondary to oral HSV infection but can be difficult to distinguish from candidal oesophagitis; keratitis, often caused by auto-inoculation from oral lesions; and viraemic spread to involve the lungs, liver or CNS. HSV pneumonitis may follow oral or genital HSV, either from contiguous spread from the oropharynx (often following intubation for other reasons) or viraemia.9 If the pneumonitis is secondary to contiguous spread then it is almost always due to HSV type 1, there are localized (focal or multifocal) lesions on chest X-ray, and only rarely does infection spread to the liver or other organs. If pneumonitis follows viraemic spread, however, then either HSV-1 or HSV-2 may be responsible, the chest X-ray shows diffuse infiltrates, (indistinguishable from CMV pneumonitis) and infection commonly involves other organs.

Diagnosis

Confirmation of HSV infection may be undertaken by examination of appropriate specimens (samples from lesions or oropharyngeal and endotracheal specimens if pneumonitis is suspected) with a rapid method such as direct electron microscopy (which will not distinguish one herpesvirus from another) or monoclonal antibody staining for viral antigens. Samples should also be cultured; the viral load is usually heavy and HSV will produce a cytopathic effect in appropriate tissue culture within 48 h.

culture-positive) was significantly reduced in those patients given acyclovir 800 mg daily; significantly lower rates of herpes labialis, intraoral ulcers (excluding those on the soft palate which were not reduced) and acute necrotizing ulcerative gingivitis were seen. These results suggest a role for HSV in oral ulcers and necrotizing gingivitis in neutropenic patients.

In patients with neutropenia, the local HSV lesions of herpes labialis are more frequent and more severe than in immunocompetent individuals. The pain of herpes labialis lasts for a median of 23 days in patients with leukaemia and the lesions take a median of 35 days to heal.5,6 Multiple, large, chronic ulcers that persist for weeks or months occur and, untreated, these may spread locally to produce extensive ulceration of adjacent skin and mucous membranes. This prolonged ulceration may predispose to bacterial and fungal infections in the mouth and oesophagus and to bacteraemia. There are data that indicate that particular regimens, e.g. high-dose cytarabine, have a particular association with mucositis and bacteraemia caused by $\alpha$-haemolytic streptococci,7,8 but it is not known if this is HSV-related. In the neutropenic population, reactivations of genital HSV are less common than oropharyngeal infections but, when they do occur, they can be equally severe.

New antiviral compounds with activity against herpesviruses, the use of ganciclovir early following BMT to prevent CMV disease will also significantly reduce HSV excretion and disease.14 New antiviral compounds with activity against HSV have been introduced but, as yet, there are no studies of the use of famciclovir or valaciclovir (a prodrug of acyclovir) in immunocompromised patients.15
host, primary CMV infection, reactivation and re-infection can thus each occur and are all associated with a significant morbidity and mortality. Although the immunocompromised populations at greatest risk of CMV infection and disease are those with deficient cellular immunity, this often accompanies neutropenia during the period of maximal bone marrow suppression in patients receiving chemotherapy for malignant disease and before marrow engraftment in the BMT recipient.

In solid-organ transplant recipients (whether they are seropositive or seronegative for CMV) the most common source of virus is the transplanted organ, even in those such as liver transplant recipients who receive large volumes of (potentially infected) blood by transfusions. In contrast, the maximal risk of CMV disease in BMT recipients is associated with reactivation of their own latent virus (i.e. in seropositive recipients).

Until recently CMV was the single most important pathogen in BMT (and, indeed, other transplant) recipients, occurring in about 50% of patients. The incidence in the early post-transplant phase is now decreasing markedly as a result of the widespread use of chemoprophylaxis.

CMV disease after allogeneic BMT. Before the use of prophylaxis, the risk of CMV isolation or disease after allogeneic BMT depended upon the serological status of both the donor and the recipient. Without prophylaxis, in about 70% of seropositive recipients CMV isolation from reactivated latent virus can be detected. Theoretically, some cases might be the result of reinfection from a second strain derived from a seropositive donor, but the incidence of CMV isolation in seropositive recipients who receive marrow from seropositive donors is no higher than in seropositive recipients who receive seronegative marrow. Furthermore, CMV disease correlates with a deficiency in CMV-specific class I HLA-restricted CD8+ cytotoxic T lymphocytes and CD4+ cells and there appears to be some degree of protection from CMV disease if the BMT donor is seropositive, suggesting adoptive transfer of CMV immunity from such T cells from the donor.

Before the use of CMV-seronegative transfusions, 40-60% of seronegative recipients of allogeneic BMT from seropositive donors developed CMV infection. A though in one series approximately one-quarter of seronegative recipients of sero negative marrow also developed primary CMV infection, this probably resulted from the transfusion of CMV-infected blood products. When screened CMV-seronegative blood products are exclusively used in CMV-seronegative recipients of seronegative marrow, the incidence of CMV disease is reduced to 3-6%.

Multivariate analysis of the risk factors for CMV disease among BMT recipients has shown that the incidence also increases with increasing age, in those who develop graft-versus-host disease (GvHD), and, perhaps, with use of cyclosporin conditioning therapy. The greatest predictor of disease (relative risk of 5.5), however, was CMV viraemia. In another study, isolation of CMV from throat, urine or blood after BMT preceded CMV disease in 78% of cases. CMV recovery from any site had a positive predictive value of 52% for disease with CMV, viraemia having a 68% positive predictive value.

CMV disease after autologous BMT. After autologous BMT, a seropositive patient has a similar 40-61% risk of having CMV isolated by day 100 as in the allogeneic setting; for the seronegative patient the probability is 23%. However, autologous recipients have a much lower incidence of CMV disease than allogeneic transplant recipients: by day 200 post-transplant the incidence is 11% for seropositive patients and 8% for seronegative patients. Others have reported even lower rates of pneumonia, of 1-6%. Pathogenesis

CMV can cause direct lytic infection of cells and tissue damage but there is considerable evidence that immunologically mediated damage may be the major pathogenic mechanism of CMV pneumonitis. The amount of CMV per gram of lung tissue does not correlate with the duration or severity of pulmonary disease or with the outcome.

Diagnosis

Given the mortality attached to CMV disease, every attempt should be made to obtain the diagnosis early in the clinical course of disease. This not only allows therapy to be started promptly but also prevents unnecessary (and potentially toxic) therapy in those without CMV disease.

The quantity of CMV in the blood correlates with the likelihood of developing CMV disease in BMT recipients but high viral loads, although temporally associated with disease, provide no prognostic information.

Conventional viral cultures and demonstration of cytopathic effect in fibroblasts is the traditional way of determining the presence of virus and risks of disease: such cultures from tissues, bronchoalveolar lavage (BAL) fluid, etc., are the gold standard for invasive disease. A
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decision regarding invasive procedures for pneumonitis (e.g., fibre-optic bronchoscopy, transbronchial biopsy, open lung biopsy) can be difficult, however, since many patients are severely thrombocytopenic. Cytopathic effects take several weeks to be observed in standard tissue culture and the shell vial technique, which increases the infectivity of the viral inoculum by centrifugation and detects an immediate early antigen of CMV by immunofluorescence within 48 h, has superseded it.

Early detection of viraemia can be made by an antigen assay or by the polymerase chain reaction (PCR). The antigen assay detects a CMV structural late antigen in white blood cells and the number of positive cells correlates with the development of symptomatic disease within a week or so.\(^35\) PCR can also be used for the detection of CMV in a variety of specimens, including blood, plasma and extracts of mononuclear cells, and shows improvements in predictive value over culture.\(^36–38\)

Prophylaxis for CMV (see below) is not completely effective and so patients on prophylaxis should still be monitored for CMV. Weekly sampling is suggested and for BMT recipients blood is the preferred site for monitoring. The utility of assays for CMV load in neutropenic cancer patients has not yet been determined.

Management

The best management strategy for CMV infection and disease in the immunocompromised individual depends upon several factors: the diagnostic tests available; the risk of disease; and the likely outcome of disease. For BMT recipients the risks of disease are high and the outcome is poor, for solid-organ transplant recipients the risks are also high but the outcome is usually good, whereas cancer patients with neutropenia are at low risk of CMV disease. The different strategies available are various forms of prevention and prophylaxis, and treatment of established disease. Traditional modes of prevention have been to administer a prophylactic regimen to a large population of patients, regardless of the degree of risk. Another approach, termed ‘pre-emptive therapy’, is only to give prophylaxis to those at greatest risk for development of disease.

Prevention. (i) Seronegative organs and blood products. The use of CMV-seronegative organs and blood products eliminates most disease in CMV-seronegative BMT recipients.\(^26,28\) Given that the cells transmitting CMV are thought to be the leucocytes, high efficacy PALL in-line filters designed to remove leucocytes from blood products have also been studied and seem to be an effective alternative to screened seronegative blood products. The latter method may have the added advantage of preventing transmission of other leucocyte-associated herpesviruses, such as human herpesvirus 6 and Epstein-Barr virus. These methods have virtually eliminated the risk of CMV disease when both donor and recipient are CMV seronegative. Hence, at present, the problem of CMV disease in BMT recipients is largely limited to those at risk of reactivating latent virus (or of secondary infection).

(ii) Immunoglobulin. There is evidence from both experimental infections and natural human infection that virus-specific antibody can fulfil an important function in host defences against CMV and passive immunization has been studied in some transplant patients. In renal transplant patients who were donor-positive/recipient-seronegative (D+R–), intravenous (iv) immunoglobulin reduced the incidence of CMV disease by almost two-thirds.\(^39\) In liver transplantation, however, there was no difference between the iv immunoglobulin and placebo recipients in the D+R– group.\(^40\) In BMT recipients iv immunoglobulin and CMV-specific immunoglobulin are not effective alone as CMV prophylaxis, although iv immunoglobulin reduces the incidence of GvHD.

(iii) Antiviral prophylaxis. Regardless of the donor’s serostatus, recipients who are seropositive have an incidence of CMV infection approaching 70% in the first 100 days after transplantation. This group of patients has been used for trials of antiviral prophylaxis against CMV disease. Prophylaxis may use low potency agents such as acyclovir and immunoglobulin or high potency drugs such as ganciclovir.

The use of acyclovir is still controversial in the prevention of CMV in BMT recipients. In a non-randomized, placebo-controlled trial, 86 seropositive recipients were given iv acyclovir in doses of either 250 or 500 mg/m\(^2\) every 8 h from 5 days before to 30 days after transplantation.\(^41\) The group given the higher dose had a significantly lower incidence of CMV infection, invasive disease and transplantation-associated mortality.

In another recent European study allogeneic BMT recipients were given high-dose iv acyclovir or oral acyclovir for the first 30 days after transplantation (when HSV reactivation is most likely) and then oral acyclovir or placebo until day 210 (a further 6 months).\(^42\) Although there was a decrease in CMV infection and viraemia and improved survival in the group given iv acyclovir followed by oral acyclovir, compared with those given oral acyclovir and then placebo, questions have been asked about the administration of ganciclovir to some of these patients and a lack of protection from primary donor-mediated disease. The lowered mortality in the high-dose recipients was not due to less CMV disease but less infectious disease generally: these other infections may be a result of CMV-induced immunosuppression, which is itself lessen by acyclovir.

For CMV-positive patients or recipients of CMV-positive BMT, the best prophylaxis results have been obtained by treatment of all patients who might develop CMV disease with high-potency anti-CMV compounds such as foscarnet or ganciclovir. These drugs are, however,
much more toxic than acyclovir, ganciclovir in particular causing troublesome neutropenia. Goodrich et al.\(^{43}\) gave ganciclovir 5 mg/kg bd iv for 5 days and then once daily until day 100, and produced a markedly lower incidence of CMV infection (P < 0.001) and CMV disease (P < 0.001) compared with a control group. Similar results have been obtained with iv ganciclovir given at a dose of 2.5 mg/kg tds for 1 week pre-transplant and then at a dose of 6 mg/kg on 5 days each week, starting after engraftment and continuing until day 100 post-BMT.\(^{44}\) In neither study was there any difference in survival between the treatment and control groups, but in each there was a high incidence of neutropenia. The study by Goodrich et al.\(^{43}\) noted a longer duration of neutropenia and a significantly increased risk (4.3-fold) of bacterial infection associated with this long duration of ganciclovir administration. These studies were, however, undertaken before the widespread use of granulocyte stimulation factors and an understanding of how the use of granulocyte or granulocyte–macrophage colony-stimulating factor might impact on the clinical benefits of ganciclovir prophylaxis remains uncertain.

Ganciclovir has been directly compared with acyclovir in liver transplant recipients but not in BMT patients.\(^{45,46}\) In both studies the use of ganciclovir (whether used alone or with acyclovir) was better than acyclovir alone in terms of CMV disease, but was not associated with any improvement in survival, probably as a result of the neutropenia and risk of other infections consequent upon long-term ganciclovir use.

A nother problem of the use of ganciclovir prophylaxis is a delay in reconstitution of protective immunity and hence the occurrence of late CMV disease after discontinuation of ganciclovir on day 100 or 120.

(iv) Adoptive immunotherapy. A adoptive immunotherapy is a novel method for reconstituting the cellular immune response to CMV in an immunodeficient host.\(^{47}\) Initial studies have been performed in allogeneic BMT recipients: CD8\(^+\) CMV-specific cytolytic T-lymphocyte clones are isolated from the bone-marrow donor, cultured in vitro and given to the recipient. A n initial clinical trial has shown that CMV-specific immunity may be reconstituted and CMV pneumonia prevented.\(^{48}\)

Pre-emptive therapy. The use of antiviral therapy at the first sign of CMV excretion but before there are clinical signs of CMV disease has been termed pre-emptive therapy.\(^{49}\) Two studies have been undertaken in BMT recipients. CMV-seropositive BMT recipients who excreted CMV (detected by culture) from throat, blood, urine or B A L fluid at 16–80 days post-transplant were given ganciclovir until day 100. CMV disease developed in 1/37 (3%), as compared with 15/35 (43%) of those given placebo.\(^{14}\) Ganciclovir also rapidly eliminated CMV excretion and was accompanied by a significantly lower transplantation-associated mortality. In another study,\(^{50}\) the administration of ganciclovir until day 120 post-transplantation to patients with a positive CMV culture from B A L fluid on day 35 post-BMT showed a similar reduction in CMV disease (25% vs. 70%) and in CMV pneumonitis. Neutropenia was the only significant side effect in both studies. Giving ganciclovir pre-emptively depends upon the sensitivity, cost and convenience of the tests for virus.\(^{14}\) In both the studies quoted above, CMV disease was diagnosed in 12% or 13% of the population in the absence of positive surveillance cultures (whether from B A L, blood, urine or throat washings). This suggests that the use of early-treatment strategies based on culture results may be only about 50% effective in preventing CMV disease. Although viraemia is also a risk factor for CMV disease in recipients of autologous BMT, there has as yet been no study of ganciclovir therapy in this group of patients.

Treatment. O nce CMV pneumonia occurs, the mortality in both allogeneic and autologous BMT patients is around 80% and antiviral drug monotherapy has no impact on this mortality rate.

(i) Viral monotherapy. O nly one of eight BMT patients with CMV pneumonia survived after acyclovir monotherapy.\(^{5}\) and although ganciclovir has a clear antiviral effect in a similar group of patients, the survival rate was equally poor.\(^{5}\) Foscarnet monotherapy is similarly ineffective: in one study all 15 patients with proven CMV pneumonia died.\(^{51}\) In all studies of monotherapy with antiviral agents, the survival rates have been similar to those in patients who received no treatment.

(ii) Combination of antivirals and immunoglobulin. Because CMV pneumonia seems related to both CMV infection and immunological factors, attempts were made to improve these responses by combination of antiviral drugs with iv immunoglobulin. Better results, with 6-week survival rates ranging from 31% to more than 80%, have been obtained with combinations of ganciclovir and iv immunoglobulin in BMT recipients.\(^{52-56}\) The 6-month survival rates are approximately 40% after such combination therapy.

Monitoring the response to therapy should be undertaken and failure to eliminate CMV from B A L fluid (as assessed by antigenaemia or PCR) within 21 days is suggestive of ganciclovir resistance. Ganciclovir resistance is usually associated with a mutation in the UL97 gene, which encodes a protein kinase that phosphorylates ganciclovir and acyclovir. Although there are no published data to support the use of foscarnet when clinical resistance to ganciclovir is suspected, most BMT centres would change to foscarnet (40–60 mg/kg tds) at this point. A close watch has to be kept for the renal toxicity of foscarnet especially for patients taking concomitant cyclosporin A.

Conclusions. The optimal time for starting and the duration of use of antiviral drugs against CMV disease in
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BMT patients has still not been determined but may well involve the use of low-risk, low-efficacy prophylaxis for all patients followed by monitoring for CMV antigenaemia or nucleic acid (by PCR) to direct the prompt initiation of pre-emptive high-efficacy antiviral therapy. Other strategies involve switching from acyclovir prophylaxis to ganciclovir when marrow engraftment has occurred (and the neutropenia induced by ganciclovir is less problematical) or the use of ganciclovir alone (either pre-emptively or as prophylaxis from the time of engraftment).

Human herpesvirus type 6

Human herpesvirus type 6 (HHV-6) is a typical enveloped herpesvirus that occurs in two variant forms, 6A and 6B, which can be distinguished by their genome size. It is a lymphotropic virus that is extremely prevalent: almost all children have been infected by the age of 2 years and 30% of adults excrete the virus constantly from their throats.

In normal children, primary infection with the virus (almost always HHV-6B) may cause exanthem subitum (roseola infantum) but is often manifest merely as fever, perhaps with febrile convulsions.

In BMT recipients HHV-6 has been implicated in a variety of clinical presentations, usually occurring at about the same time post-transplant as CMV (therefore often beyond the period of neutropenia). Interstitial pneumonitis, encephalitis, rash and fever, and marrow suppression in BMT recipients have all been associated with HHV-6 infection.

Of the anti-herpesvirus drugs available, ganciclovir has the greatest potency against HHV-6 but there are no data on the clinical response of HHV-6 infections to drug therapy.

Varicella zoster virus

Before the use of acyclovir as prophylaxis, varicella was a classic opportunistic infection in children with lymphoma or acute leukaemia or following BMT, sometimes becoming disseminated to the lungs, liver or CNS. Untreated, such infections had a mortality of 7-30%.

Varicella-zoster virus (VZV) disease in adults with leukaemia or post-transplantation (solid organ) was occasionally primary varicella but more usually reactivation of latent virus to cause herpes zoster, which disseminated to the skin or viscera in 25% and 13% of instances respectively. Such episodes typically occur 3 months or more after transplantation (median time 5 months) and are not usually seen while the patient is neutropenic. Subclinical reactivation of VZV is probably frequent after transplantation (19% of patients have VZV DNA detectable in blood by PCR after BMT).

Prevention of varicella

One important way to prevent primary acquisition of VZV in the immunosuppressed patient is to prevent contact with persons with chickenpox or herpes zoster. The serological status of the patient (especially if a child) should be determined before starting immunosuppressive therapy. For the seronegative child, the parents and school need to be fully informed and asked to follow a formulated plan of action.

Passive immunization with VZV immunoglobulin has been shown, in comparison with historical controls, to reduce the severity of disease and the incidence of complications such as pneumonitis and encephalitis in a number of different immunocompromised populations. One vial per 10 kg body weight should be administered within 96 h of exposure to a seronegative child who has household, playmate or hospital contact with varicella or herpes zoster. If exposure does occur, the incubation period of varicella in the seronegative neutropenic child is longer than usual and the child should be considered at risk of varicella for up to 28 days. The use of acyclovir as post-exposure prophylaxis for varicella has never been investigated in the immunocompromised host. In normal children with household exposure administration of acyclovir for 7 days (starting between day 7 and 9 after exposure) does reduce the severity of disease manifestations. If shown to be of advantage in immunocompromised patients, such an approach would have a potential cost-advantage compared with the use of VZV immunoglobulin.

A varicella vaccine derived from the Oka strain of live attenuated VZV has been studied in children with acute lymphoblastic leukaemia. Seronegative children were given two doses of vaccine, 3 months apart, during the period of maintenance therapy for their leukaemia. Ninety-six percent had an antibody response and the incidence of varicella after household exposure was significantly reduced to about 12% in the vaccinated group compared with the estimated normal risk of 80-90%. In 75% of recipients the antibody response persists for at least 10 years. There is no increased risk of herpes zoster developing in the vaccinated children.

Prevention of herpes zoster

Antiviral prophylaxis with acyclovir is not routinely administered with the aim of preventing VZV reactivation since such reactivation occurs relatively late after transplantation and only affects a relatively small proportion of seropositive individuals, who cannot be identified as being at particular risk by their serological titre. A cyclovir or ganciclovir prophylaxis aimed at prevention of HSV or CMV disease, however, has the additional benefit of significantly reducing the incidence of VZV disease.
Treatment

Treatment of VZV disease in immunocompromised patients is with iv acyclovir at a high dosage of 10 mg/kg tds. The use of oral acyclovir and of the new oral antiviral prodrugs, famciclovir and valaciclovir has not been studied in this setting.

Respiratory viruses

There has been an increased recognition of the importance of respiratory viruses after BMT in recent years, perhaps reflecting an improvement in culture techniques. They may be acquired either nosocomially or in the community at any time following transplantation but, when they present clinically during the period of neutropenia shortly after the transplant, they have often been acquired before transplantation surgery. Patients may have upper or lower respiratory tract symptoms and respiratory viruses are now appreciated as important causes of pneumonia in adult BMT patients, causing many of the previously categorized ‘idiopathic’ pneumonias.71,72 The commonest respiratory viruses are respiratory syncytial virus (RSV), rhinoviruses, parainfluenza viruses and influenza A virus.

Respiratory syncytial virus

RSV is a paramyxovirus that causes winter epidemics of bronchiolitis, pneumonia and laryngitis in about 20% of infants and school-age children. Although up to 5% of the adults who come into contact with them will become infected, these infections are usually limited to the upper respiratory tract. In contrast, RSV causes devastating outbreaks of disease in adult BMT recipients,73–76 after organ transplantation and in patients undergoing chemotherapy for leukaemia.77 The importance and severity of RSV in these adult populations is becoming more widely recognized. In adult patients with leukaemia, during a period when RSV was prevalent in the community, 10% of acute respiratory illnesses were caused by RSV. In this study and in studies in BMT,75 at least a third of infections were nosocomial and could be prevented by protective isolation.

Illness is characterized by upper respiratory symptoms (sore throat, rhinorrhoea, otitis and sinusitis) followed by cough (typically productive), fever, dyspnoea and hypoxia in those with pneumonia. The presence of otalgia and sinusitis are useful discriminatory signs against infection being due to CMV. Pneumonia is more commonly seen in BMT recipients who are still neutropenic when infected and neutropenic patients developed pneumonia within a mean of 3 days after RSV was first identified (compared with 6 days for those infected after engraftment). Untreated, death occurs in nearly 80% of those who develop RSV pneumonia.

Early diagnosis is critically important in these groups and the diagnosis must be considered when a diffuse interstitial pneumonitis occurs in a BMT recipient or any immunocompromised adult, especially during the late winter/early spring months, when RSV is prevalent in the community. Respiratory secretions (in adults BAL is the optimal clinical specimen) should be sampled for viral culture (by shell vial) and rapid RSV antigen detection by direct immunofluorescence. Serology is usually unhelpful in immunocompromised patients because of the inconsistency of the antibody response. Histology at autopsy of those dying with pneumonia showed multinucleated syncytial cells and giant cells with intracytoplasmic viral inclusions, confirmed as RSV by monoclonal antibodies.

Treatment. Treatment of RSV in this group of patients has not been evaluated in a controlled fashion, although there is some evidence that ribavirin aerosol, administered via a small particle aerosol generator from a flask containing 20 mg ribavirin/mL water over 18–20 h/day, may improve survival.

In a study from Seattle,14/18 (78%) of patients with pneumonia died and the mortality was no higher in those with disease pre-engraftment. There was no opportunity to determine formally the effect of ribavirin, given as 6 g by aerosol for 18 h daily, on the outcome, since there was no control group. The ribavirin recipients did better but this may not have been a beneficial effect of the drug, rather that those given ribavirin were less seriously ill.

A study of 19 BMT patients infected with RSV at the MD Anderson Cancer Center, Texas, USA, found that seven patients had tracheo-bronchitis and 16 (including four with tracheo-bronchitis) developed pneumonia. Some patients in this series were treated with a combination of daily aerosolized ribavirin and iv immunoglobulin (500 mg/kg on alternate days). When such therapy was initiated more than 24 h before the onset of respiratory failure (which required mechanical ventilation) then only two of nine patients died. A ll patients who were not treated or who were treated after the onset of respiratory failure, died.

Outcome in BMT recipients depends upon engraftment status, presence of lung infiltrates, and respiratory status (including supplemental O₂). Once respiratory failure and the need for mechanical ventilation has developed then antiviral therapy is of no use—mortality approaches 100%. It has been recommended that all patients should have a culture for RSV taken before BMT and that ribavirin therapy should be given to those with positive cultures but, given the length of time that it can take for virus to be detected in tissue culture and the short incubation period of RSV (a mean of 5 days), the practicality of this approach has been questioned.

Aquisition of RSV is often nosocomial with the virus carried on hands and found on surfaces. In paediatric
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patients at least, the wearing of gloves, masks and gowns will reduce the risk of RV transmission. In the event of an RV case, sources of infection should be sought among other patients and ward staff in order to prevent further transmission and to institute appropriate control measures and antiviral therapy instituted as promptly as possible to those at most risk.

Parainfluenza viruses

Two studies of BMT recipients have shown parainfluenza virus infections in about 3% of individuals. A review of 265 adult BMT recipients revealed that parainfluenza virus type 3 had caused six cases of severe lower respiratory tract infection. These infections were seen in both allogeneic and autologous transplant recipients and occurred both early, during the period of post-transplantation neutropenia, and late after transplantation. The patients had symptoms and signs of lower respiratory tract infection, generally, with bilateral chest X-ray infiltrates; some also had upper respiratory tract infection symptoms. The mortality among the patients with pneumonia was 50% and there were cytoplasmic viral inclusions consistent with parainfluenza infection. All the patients who died also had fungal pneumonia and so the cause of death may not have been purely due to parainfluenza virus. In another study 2% of each of 673 children and 580 adults who underwent BMT had documented parainfluenza infection. Seventy percent of these 27 patients had lower respiratory tract infection and there was a 32% mortality. The severity of the infection does not correlate with the type of transplant or the time of infection.

Influenza A virus

A study of influenza A infections in immunocompromised patients during two periods of epidemic influenza A revealed a course of disease comparable to that seen in immunocompetent individuals, although two of the three patients with more serious disease were BMT recipients who developed influenza during the pre-engraftment period. Treatment of immunocompromised patients with amantadine can result in drug-resistant viruses emerging rapidly and being shed for prolonged periods.

A denoviruses

A denovirus infections have been reported in patients with both cellular and humoral immune defects, including BMT recipients. Typically such infections occur 1–3 months after organ transplantation, at a time when most patients are no longer neutropenic. The infections may be transmitted by the respiratory route. A denoviral shedding in the urine or throat is found in 4–21% of BMT patients but only 1–6.5% develop disease. A denoviral faecal shedding is also considerable, and some types cannot be cultured.

A variety of different clinical syndromes may occur, of which the most common are hepatitis and pneumonia. Hepatitis presents with fever, vomiting and anorexia and the hepatitis is characterized by liver cell necrosis and relative sparing of the portal tracts. Some hepatitis patients have lung involvement also; this may be unilateral or bilateral and can be fulminant or indolent. The overall mortality of adenovirus infection in BMT patients is approximately 60%.

During a period when adenoviruses were prevalent in the community, they were implicated in a significant proportion of the gastrointestinal infections occurring during the early (neutropenic) post-BMT period. Confirmation of the diagnosis is usually by viral isolation or antigen detection in tissues but there is no specific therapy available.

Enteroviruses

Considerable morbidity and some mortality were reported during an outbreak of diarrhoea caused by coxsackievirus A1 during the engraftment period following bone marrow transplantation. The diarrhoea was difficult to distinguish from the enteropathy associated with GvHD.

Rotavirus gastroenteritis

Rotavirus gastroenteritis in the immunocompromised patient can be either an acute illness (as seen in infantile diarrhoea in the immunocompetent individual) or a more chronic illness. Although the latter may be a severe problem in BMT recipients, such infections do not typically occur during the neutropenic period.

BK virus

BK virus (named after the initials of the patient from whom it was first isolated) is a polyoma virus. Antibodies to the virus are found in about three-quarters of adults and it appears that the virus is usually acquired in infancy. Most primary infections are asymptomatic or associated with minimal upper respiratory tract symptoms. The virus then establishes latency in renal tissue and during immunosuppression may be reactivated, leading to viruria.

BK viruria occurs in about 50% and <10% of allogeneic and autologous BMT recipients respectively. It is only seen in those who are seropositive before transplantation (hence it is a reactivation of latent BK viral infection) and is usually found during the second or third month after transplantation. It is often completely asymptomatic but is significantly associated with the development of late-onset prolonged (>7 days) haemorrhagic cystitis.
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