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Recent Advances in Cytomegalovirus: An Update on Pharmacologic and Cellular Therapies

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A B S T R A C T

The 2015 Tandem American Society for Blood and Marrow Transplantation/Center for International Blood and Marrow Transplant Meetings provide an opportunity to review the current status and future perspectives on therapy for cytomegalovirus (CMV) infection in the setting of hematopoietic stem cell transplantation (HSCT). After many years during which we have seen few tangible advances in terms of new antiviral drugs, we are now experiencing an exciting period of late-stage drug development, characterized by a series of phase III trials incorporating a variety of novel agents. These trials have the potential to shift our current standard therapeutic strategies, which generally involve pre-emptive therapy based on sensitive molecular surveillance, towards the prophylactic approaches we see more generally with other herpes viruses such as herpes simplex and varicella zoster. This comes at a time when the promise of extensive preclinical research has been translated into encouraging clinical responses with several cellular immunotherapy strategies, which have also been moved towards definitive late-stage clinical trials. How these approaches will be integrated with the new wave of antiviral drugs remains open to conjecture. Although most of the focus of these cellular immunotherapy studies has been on adaptive immunity, and in particular T cells, an increasing awareness of the possible role of other cellular subsets in controlling CMV infection has developed. In particular, the role of natural killer (NK) cells is being revisited, along with that of γδ T cells. Depletion of NK cells in mice results in higher titers of murine CMV in tissues and increased mortality, whereas NK cell deficiency in humans has been linked to severe CMV disease. We will review recent progress in these areas.

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ADVANCES IN PHARMACOLOGIC THERAPIES

Current Approaches

Over the past 2 decades, both prophylaxis and preemptive therapy have been used to prevent CMV disease in the HSCT setting [1]. Although preemptive therapy is most commonly used, prophylaxis is favored by some centers for high-risk patients, such as recipients of unrelated, HLA-mismatched or cord blood products. Although both strategies are effective for prevention of CMV, they rely on available drugs with significant toxicities, including marrow toxicity for ganciclovir, valganciclovir, and cidofovir, and renal toxicity for foscarnet and cidofovir [2,3].

The treatment of CMV disease after HSCT typically consists of ganciclovir at induction doses for 2 to 3 weeks, followed by maintenance dosing until all signs and symptoms are undetectable. When cytopenias are present, foscarnet is used as alternative. Valganciclovir is sometimes used after an initial response is documented, provided that there is good oral intake and adherence to the regimen; however, no systematic evaluations of this approach exists. Although CMV gastrointestinal disease can be treated with an antiviral drug alone, recommendations for CMV pneumonia include the addition of intravenous immunoglobulin [2,4]. Drug-resistant CMV disease is rare after HSCT but should be suspected in patients with poor clinical or virologic responses and pre-exposure to the antiviral drug used. Patients who are on antiviral drugs and who have had viral load increases for more than 2 weeks may have resistance. If drug resistance is suspected, genotypic testing and switching to an alternative drug is recommended as first-line approach [2,5]. Viral load can be used to monitor the response to treatment. In patients with documented drug resistance or those who are critically ill, often few options exist and none are

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supported by high-quality data. Novel agents described below may be available for use in some situations.

Future Approaches

Because of the safety profile of currently available drugs, efforts have been made in developing new compounds with similar or improved efficacy and improved toxicity. Also, several presently available drugs have been reported to have anti-CMV activity in vitro. The following summarizes new antiviral agents being evaluated in clinical trials in HSCT recipients.

Maribavir, a UL97 protein kinase inhibitor, is an oral drug with specific activity against CMV [6]. A phase II dose-ranging study in HSCT recipients showed that CMV infection or disease was reduced at all 3 dose levels tested, but a subsequent phase III study that used the lowest dose (100 mg twice daily) failed to prevent CMV disease [7]. The failure of the study was primarily attributed to the dose used in that study [8]. Maribavir has in vitro activity against ganciclovir- or cidofovir-resistant CMV, and small case series suggest a possible clinical benefit at higher doses [9]. Therefore, 2 ongoing phase II dose-ranging trials are examining higher doses of maribavir treatment of refractory or resistant CMV disease (clinicaltrials.gov NCT01611974) and as preemptive therapy (EudraCT: 2010-024247-32).

Letermovir (AIC-246), a CMV terminase inhibitor, is another highly selective anti-CMV agent [10,11]. The drug can be given orally or intravenously and is highly active against wild-type and drug-resistant CMV in vitro. In vivo experience for multidrug-resistant CMV disease is limited [12]. A phase II dose-escalation study in CMV-seropositive HLA-matched HSCT recipients showed a reduction of prophylaxis failure (defined as drug discontinuation due to CMV infection or disease or any cause) in patients receiving the 240 mg of letermovir compared with those receiving placebo [13]. The drug was tolerated well, with similar adverse event rates in letermovir and placebo recipients. A phase III randomized multicenter trial is currently ongoing using a similar trial design as the phase II trial (clinicaltrials.gov NCT02137772).

Brincidofovir (CMX-001) is a new broad spectrum antiviral agent that has in vitro activity against herpesviruses, polyomaviruses, adenoviruses, papillomaviruses, and variola virus [6]. It is a lipid-conjugated nucleotide analogue of cidofovir that has a high oral bioavailability and long half-life, allowing twice weekly oral dosing. In contrast to its parent compound, brincidofovir is not a substrate for the human organic anion transporters and, therefore, has significantly reduced potential to cause renal toxicity. A phase II dose-escalation study in HSCT recipients showed a reduction of CMV infection or disease in patients receiving brincidofovir at doses of 200 mg per week for prophylaxis started at engraftment [14]. The most common side effect was diarrhea in patients receiving CMX001 at doses of 200 mg weekly or higher. It was dose limiting at 200 mg twice weekly. There was no difference in renal or hematologic adverse effects between brincidofovir and placebo recipients. A phase III randomized multicenter trial of brincidofovir at a dose of 100 mg twice weekly is currently ongoing using a similar trial design as the phase II trial (clinicaltrials.gov NCT01769170).

Leflunomide is a Food and Drug Administration–approved drug for the treatment of arthritis with documented activity against several viruses, including CMV and BK virus [15]. Leflunomide has been used in salvage situations for CMV disease with mixed results [16]; however, no systematic evaluation of the efficacy and toxicity of leflunomide either as mono- or combination therapy has been performed.

Finally, artesunate is an antimalarial agent that also has broad antiviral activity in vitro against herpes viruses [17], hepatitis viruses, and human immunodeficiency virus because of its ability to downregulate NF-κB or Sp1 pathways [18]. There are anecdotal reports of its effectiveness in patients with complicated CMV infection, including multidrug-resistant CMV [19]; however, no systematic evaluation of the efficacy and toxicity of artesunate for CMV treatment has been performed.

Future Perspectives

Preemptive antiviral therapy substantially reduced the incidence of CMV disease after HSCT in the past 20 years. Several new drugs are now in advanced stage of clinical evaluation and may be available for more effective and less toxic prevention of CMV in HSCT recipients. Studies are also needed to determine whether these drugs can be used in combination to reduce mortality of CMV pneumonia.

ADVANCES IN T CELL THERAPIES

Because the primary risk factor for CMV infection after HSCT is considered to be a deficit in number and function of CMV-reactive T cells [20], a number of investigators have addressed the possibility that adoptive transfer of donor-derived (and, in some cases, third-party) CMV-reactive T cells will hasten reconstitution of protective pathogen–specific immunity, potentially reducing the infective burden and associated treatment costs [21]. Derivation of a therapeutic cellular product is technically easiest when the original stem cell graft donor has pre-existing immunity to CMV. In these cases, direct selection of virus-specific T cells, or expansion of such cells in ex vivo, is usually feasible. Most of the early demonstrations of proof of concept relied on an ex vivo expansion step, limiting more widespread clinical application [22,23]. Subsequent refinements in culture conditions allowed more rapid cell expansion [24-27]. More recently, increasingly robust strategies for direct selection of virus-specific T cells from seropositive donors have been developed, including selection after restimulation with viral peptides according to secretion of IFN-gamma or up-regulation of cell surface activation markers [28,29], or direct selection of unstimulated cells based on binding of class I HLA-multimers [30,31]. Each strategy produces a therapeutic product that differs in terms of cellular composition, purity, antigen specificity, and functional characteristics. Application in subsequent phase I and II studies has also introduced further variation in terms of the cell doses employed, and the timing of and indication for intervention (eg, prophylactic, preemptive, or for clinically “resistant” infection). Nevertheless, most clinical studies reach a broadly similar conclusion: immunity can be restored in the absence of significant toxicity and with a low risk of induction of graft-versus-host disease (GVHD) [32]. Of course, early phase studies may be influenced by selection biases, and exclusion of those with clinically significant active GVHD is an obvious bias of these early studies. Furthermore, there are data to suggest that immune reconstitution after HSCT is dependent to some degree on the frequency of CMV-specific T cells in the donor graft. Because low precursor frequency correlates with failure to generate a therapeutic product in some cases, a further bias is introduced in uncontrolled studies. These

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