Ganciclovir-Resistant Cytomegalovirus in Organ Transplant Recipients

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Ganciclovir-resistant (GanR) cytomegalovirus (CMV) is an emerging clinical problem in organ transplant recipients, particularly recipients of kidney and pancreas and lung transplants. GanR CMV, a late posttransplantation complication, is observed predominantly among CMV-seronegative recipients of organs from seropositive donors, especially among recipients receiving intensive immunosuppression and having prolonged exposure to ganciclovir. Given the limitations of current diagnostic methods, if GanR CMV is clinically suspected, empirical treatment with intravenously administered foscarnet should be used in conjunction with reductions in immunosuppressive therapy and possibly CMV hyperimmune globulin. Better diagnostic tools and newer, less-toxic antiviral agents with different mechanisms of action are urgently needed to decrease the morbidity associated with this complication in organ transplant recipients.

Cytomegalovirus (CMV) remains an important pathogen in organ transplant recipients, and ganciclovir has been the antiviral agent of choice both for prevention and treatment of CMV disease. Shortly after the introduction of ganciclovir in the late 1980s, sporadic cases of ganciclovir-resistant (GanR) CMV were reported in severely immunocompromised patients, usually after prolonged exposure to ganciclovir [1]. During the AIDS epidemic, the development of ganciclovir resistance was reported among patients with AIDS who were receiving prolonged ganciclovir therapy for CMV retinitis. Furthermore, studies demonstrated that in vitro resistance to ganciclovir was associated with clinical progression of CMV disease [1–4].

In contrast, during this same period, only isolated cases of GanR CMV were reported among solid-organ transplant (SOT) recipients. However, more recently, with the advent of more widespread use of oral ganciclovir and use of more-intensive immunosuppressive strategies, there has been increased recognition of ganciclovir resistance as a clinical problem in organ transplant recipients.

In the present article, I summarize the current understanding of the pathogenesis, clinical manifestations, diagnosis, and management of GanR CMV in SOT recipients. My goal is to provide to clinicians who care for SOT recipients the information necessary to promptly recognize and appropriately treat patients with suspected or documented GanR CMV. I refer readers to other sources for more-detailed discussions of the molecular virologic aspects of GanR CMV [1, 5, 6].

DEFINITION AND MECHANISM OF RESISTANCE

The “gold standard” definition of resistance to ganciclovir is dependent on the demonstration of reduced susceptibility of a CMV isolate to ganciclovir in vitro (typically, an IC_{50} >6 μM) by use of a plaque reduction assay [7]. The mechanism of resistance can best be understood in the context of the mechanism of action of ganciclovir (figure 1). Ganciclovir is a guanosine analogue that exerts its antiviral effect by inhibiting CMV DNA polymerase. To be active, ganciclovir must be converted to a triphosphorylated form; this conversion occurs via 3 sequential phosphorylation steps, the first of which is performed by a virally encoded phosphotransferase (product of UL97). The 2 subsequent phosphorylation steps are performed by cellular enzymes, and the triphosphorylated form of ganciclovir ultimately preferentially inhibits CMV DNA polymerase (product of UL54).

Mutations in UL97, UL54, or both are the major mechanisms of resistance to ganciclovir. Such mutations result in the inability of ganciclovir to effectively inhibit CMV DNA polymerase, thereby allowing for viral replication despite the presence of the antiviral agent. The mechanism of resistance is intimately associated with the development of clinical manifestations, and the management of GanR CMV in SOT recipients is complex and requires a multidisciplinary approach involving transplant surgeons, infectious disease physicians, and virologists.

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by which CMV becomes resistant to ganciclovir [5, 6, 8]. Mutations in UL97 ultimately result in decreased levels of the triphosphorylated (active) form of ganciclovir. In contrast, mutations in UL54 directly result in a mutant DNA polymerase that is less inhibited by ganciclovir and/or other antiviral compounds (i.e., cidofovir, foscarnet). CMV isolates with mutations in UL97 alone typically demonstrate lower levels of resistance to ganciclovir than do isolates with mutations in UL97 and UL54 [9]. The most common mutations in these regions (among clinically ganciclovir-resistant isolates) have been confirmed by in vitro studies to confer phenotypic resistance to ganciclovir [6].

The correlation between these genotypic alterations in UL97 and phenotypic and clinical resistance to ganciclovir has formed the basis for more-rapid resistance testing via genotypic screens for resistance [10]. The most important points regarding mutations in these regions include the following: (1) mutations in UL97 are significantly more common than mutations in UL54, (2) the majority of mutations in UL97 occur in a specific region (codons 460–607), and (3) mutations in UL54 typically are associated with higher levels of resistance to ganciclovir or cross-resistance to cidofovir or foscarnet. I refer readers to texts with more-detailed discussions of the molecular basis for resistance [5, 6, 8, 10].

**PATHOGENESIS OF AND RISK FACTORS FOR GANCICLOVIR-RESISTANT CMV**

Although the pathogenesis of GanR CMV is incompletely understood, important new insights have come from a study by Emery and Griffiths [11]. Using mathematical prediction models that were subsequently validated by in vivo studies, they showed that in the presence of ganciclovir, mutant CMV strains (i.e., GanR CMV strains) have a survival advantage, compared with wild-type CMV strains. During prolonged exposure to ganciclovir (and especially in the presence of the lower drug levels in blood that are achieved with oral ganciclovir), these resistant mutant strains become the dominant population and can ultimately lead to virologic or clinical failure in organ transplant recipients. Their models help explain several important aspects of ganciclovir resistance in CMV: (1) a high virus load provides a greater opportunity for selection of resistant mutants, (2) ganciclovir resistance rarely develops after a short duration of exposure to ganciclovir, (3) ganciclovir resistance develops more commonly after exposure to oral versus intravenous ganciclovir, and (4) phenotypic laboratory methods may underestimate the true prevalence of resistance.

Although these models help to explain several important aspects of ganciclovir resistance, they specifically focus on the virologic aspects of resistance and do not incorporate other host factors that are also likely to be important in the pathogenesis of ganciclovir resistance. On the basis of the epidemiology of GanR CMV in SOT recipients, it is likely that no single factor is likely to be responsible for the development of resistance. Otherwise, the prevalence of resistant CMV would likely be much higher than is presently observed. The fundamental condition for the development of resistance is prolonged viral replication in the presence of drug. In clinical practice, multiple factors likely need to come together in an individual patient for clinically significant ganciclovir resistance to develop. These factors include D−R− (donor-seropositive and recipient-seronegative) status, prolonged exposure to ganciclovir, potent immunosuppression, suboptimal ganciclovir levels, and high virus load. Several of these factors are interrelated, but which of the specific factors promote the development of resistance, the extent to which they do so, and the specific contribution of each factor are poorly defined at present. However, because the vast majority of organ transplant recipients with ganciclovir resistance who have been reported to date have been D−R−, the transplant population can be considerably narrowed to a subgroup in whom resistance is more likely to occur.

Another clinical variable that may be important in influencing the rate of resistance is the type of antiviral strategy used: universal prophylaxis or preemptive therapy [12–14]. In a preemptive approach, antiviral therapy is specifically targeted to patients considered to be at risk (rather than to all patients); therefore, less antiviral therapy is provided for shorter periods. Thus, theoretically, a preemptive approach might be expected to be associated with lower rates of resistance. Few studies have directly addressed this issue. However, a single, relatively small, retrospective study demonstrated high rates of ganciclovir resistance among lung transplant recipients, despite the use of preemptive therapy [15]. Adequately powered prospective comparisons of preemptive and prophylaxis strategies for patients with a high risk for antiviral resistance have not yet been performed, and, thus, the relative abilities of preemptive therapy and prophylaxis to select for resistance remain controversial.
The current hypothesis regarding the predominance of GanR CMV among patients with a D’R– status (hereafter referred to as “D’R– patients”) is that these patients generally have higher CMV loads [6] and that these higher loads are more difficult to suppress [15, 17]. In the presence of a high virus load, suboptimal drug concentrations, and absence of adequate immune response, there exists a greater likelihood for the selection and expansion of resistant mutants. Although, to date, GanR CMV has been reported most often in D’R– patients, other clinical settings that are also associated with these conditions might also be conducive to the development of resistance. For example, lung transplantation is the other clinical setting in which these conditions may also exist, thereby allowing for emergence of GanR CMV even among R+ recipients [15, 18]. Until the specific factors that lead to ganciclovir resistance can be more precisely defined, D’R– patients who have ≥1 of the additional risk factors noted above should be considered to have a greater risk for developing ganciclovir resistance.

**CLINICAL ASPECTS**

The clinical spectrum of GanR CMV among SOT recipients is broad and can range from asymptomatic viremia to symptomatic disease (including CMV “syndrome” and tissue-invasive disease) [19]. Although a study by Emery and Griffiths [11] has documented decreased fitness of mutant-resistant CMV strains in terms of replicative potential, considerable evidence suggests that resistant CMV strains can be fully pathogenic. For example, isolation of GanR CMV strains has been associated with clinical progression of CMV disease despite intravenous administration of full-dose ganciclovir [2–4, 17]. In addition, GanR CMV strains have been demonstrated in diseased tissue [20]. However, it should be noted that not all clinical failure associated with ganciclovir treatment can be attributed to resistance and that, conversely, clinical improvement can occur despite ganciclovir treatment of phenotypically and genotypically resistant CMV [15, 17, 21]. These findings emphasize the importance of host and other factors in the outcome of CMV infection. In the studies of ganciclovir resistance among SOT recipients reviewed in the present article (and for whom clinical data were provided), 20 (87%) of 23 patients experienced symptomatic infection (45% had CMV syndrome and 55% had tissue-invasive disease) with GanR CMV. With the use of routine ganciclovir prophylaxis at many transplant centers, the onset of CMV infection and disease appears to occur significantly later than it did in the era before widespread use of prophylaxis was initiated [17, 29, 36]. Accordingly, the onset of GanR CMV has been recognized as a complication that occurs relatively late after transplantation. The onset of ganciclovir resistance occurred 51–510 days after transplantation (median onset, 198 days after transplantation) (table 1). Most patients had prolonged exposure to ganciclovir (median, 118 days; range, 21–438 days), and many (12 of 19 [63%]) had received oral ganciclovir for varying periods (median, 124 days, range, 28–200 days) before resistance was first documented.

One of the most important features about the epidemiology of resistance among organ transplant recipients has been the finding that GanR CMV is seen almost exclusively in CMV-seronegative recipients of transplants from seropositive donors (D’R+) rather than in seropositive patients, at least among non–lung transplant recipients. All 16 non–lung transplant recipients with GanR CMV were D’R+ (table 1). However, only 14 (56%) of 25 lung transplant recipients were D’R+. Overall, 30 (73%) of 41 cases of GanR CMV reported to date have occurred in D’R– patients. In contrast, D’R– patients typically account for only ~20% of all transplant recipients, which suggests that D’R– status is an important risk factor for the development of ganciclovir resistance [15, 17]. These data also suggest that, at least among lung transplant patients, factors other than D’R– status may also be important in the development of GanR CMV.

In the overall IMCMIC experience (table 2), the crude mortality among patients with GanR CMV was 19%. It is uncertain to what extent this percentage reflects mortality that is directly attributable to CMV versus other host factors. In addition, a high rate of allograft loss has been seen among patients with GanR CMV [17]. Furthermore, in a large study of lung transplant recipients, GanR CMV infection was associated with reduced survival and earlier onset of bronchiolitis obliterans [18].

The incidence of ganciclovir resistance among SOT patients has not been precisely defined and appears to vary according to the specific population studied, the immunosuppressive agents and antiviral prophylaxis used, and the definitions of resistance used. Furthermore, estimates of incidence are largely based on retrospective, rather than prospective, studies and thus must be considered crude estimates rather than precise figures. Table 2 summarizes several studies that have attempted to define the incidence of ganciclovir resistance according to type of transplant. The overall incidence of ganciclovir resistance is 0%–13% and appears to be highest overall among kidney and pancreas transplant or lung transplant recipients. As previously noted, lung transplant recipients appear to be the only group of SOT recipients for whom GanR CMV occurs in CMV-seropositive patients (R+) as well as in D’R– patients. With the use of routine ganciclovir prophylaxis at many transplant centers, the onset of CMV infection and disease appears to occur significantly later than it did in the era before widespread use of prophylaxis was initiated [17, 29, 36]. Accordingly, the onset of GanR CMV has been recognized as a complication that occurs relatively late after transplantation. The onset of ganciclovir resistance occurred 51–510 days after transplantation (median onset, 198 days after transplantation) (table 1). Most patients had prolonged exposure to ganciclovir (median, 118 days; range, 21–438 days), and many (12 of 19 [63%]) had received oral ganciclovir for varying periods (median, 124 days, range, 28–200 days) before resistance was first documented.
Table 1. Overview of solid-organ transplant recipients with ganciclovir-resistant (GanR) cytomegalovirus (CMV).

<table>
<thead>
<tr>
<th>Transplant type, reference</th>
<th>No. of patients</th>
<th>CMV serostatus</th>
<th>CMV onset, no. of days after transplantation</th>
<th>Clinical manifestations of GanR CMV</th>
<th>Duration of Gan therapy before GanR CMV onset, no. of days</th>
<th>Oral Gan Outcome</th>
<th>Gan IC&lt;sub&gt;50&lt;/sub&gt;, µM</th>
<th>UL97 mutation</th>
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<td>Retinitis</td>
<td>NR</td>
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<td>Survived</td>
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<td>D&lt;sup&gt;+&lt;/sup&gt;R&lt;sup&gt;-&lt;/sup&gt;</td>
<td>NR</td>
<td>Retinitis</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>&gt;20</td>
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<td>Syndrome</td>
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<td>No</td>
<td>Died</td>
<td>NR</td>
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<td>1</td>
<td>D&lt;sup&gt;+&lt;/sup&gt;R&lt;sup&gt;-&lt;/sup&gt;</td>
<td>231</td>
<td>Enteritis</td>
<td>200</td>
<td>Yes</td>
<td>Survived</td>
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<td>Pneumonia</td>
<td>56</td>
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<td>Died</td>
<td>20</td>
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NOTE. Dates and dosages are approximate and are based on extrapolation of data from figures. Del, deletion; D<sup>+</sup>R<sup>-</sup>, donor seropositive, recipient seronegative; Gan, ganciclovir; NR, not reported; R<sup>-</sup>, recipient seronegative.

<sup>a</sup> By immediate early antigen plaque reduction assay.
<sup>b</sup> Specific mutation not specified.
<sup>c</sup> Eight patients.
<sup>d</sup> Ten patients.
<sup>e</sup> Represents median value for group.
<sup>f</sup> Converted to micromoles from reported value expressed in micrograms per milliliter.

patients have an increased risk for CMV infection and disease and that this increased risk likely results from the presence of higher virus loads and the absence of preexisting immunity to CMV. Thus, D<sup>+</sup>R<sup>-</sup> patients already possess 2 of the important proposed risk factors for development of resistance (high virus load and absence of preexisting immunity). On the basis of these observations, it is now possible to identify a subset of organ transplant recipients who have an increased risk for developing GanR CMV and for whom more-intensive surveillance, heightened clinical suspicion, and judicious use of antiviral therapy and immunosuppression are warranted.

LABORATORY DIAGNOSIS

Definitive diagnosis of ganciclovir resistance is dependent on the demonstration of reduced susceptibility of a clinical CMV isolate to ganciclovir in vitro by use of any one of a number of virologic methods. Each of the specific methods has relative
advantages and disadvantages, and more-detailed descriptions of the various methodologies have been reviewed elsewhere [1]. The assays generally can be divided into phenotypic and genotypic methods. Currently, widely clinically available assays require analysis of a clinical virus isolate. This is a major limiting factor because of the time required for virus isolation (typically, several weeks). Although modifications of current techniques have shortened the time required to obtain a result, these modified assays are not widely clinically available and thus are not commonly used to guide clinical decision-making. In addition, interpretation of the results of antiviral resistance studies (especially phenotypic studies) is difficult given the lack of standardization and variability between different laboratories. At present, assays to evaluate the phenotypic and genotypic resistance of CMV isolates are clinically available, but they are limited by the time required to obtain a result, as discussed above.

Phenotypic methods rely on the measurement of inhibition of viral growth in the presence of antiviral agents. This can be done by measuring either viral plaques, viral DNA synthesis, or viral antigen production [1]. In contrast, genotypic methods take advantage of the fact that specific mutations have been associated with phenotypic resistance to specific antiviral agents [10]. The recognition that mutations are clustered at specific codons (“hot spots”) in either UL97 or UL54 has paved the way for diagnostic screening assays [10]. These assays are based on restriction enzyme analysis of PCR products from clinical CMV isolates. Although definitive identification of mutations requires sequence analysis, many of the more commonly encountered mutations in UL97 can be detected with screening restriction enzyme assays [10]. A major advance in the area of diagnostic methods for CMV resistance has been the direct application of genotypic methods to clinical specimens, rather than to virus isolates [3]. This type of approach circumvents the need for virus isolation and theoretically can significantly shorten the time required to detect resistance. In addition, these methods appear to be more sensitive than conventional culture-based methods for the detection of resistance [37]. As these techniques evolve and become more widely clinically available, they will likely play an important role in the clinical management of SOT recipients with suspected GanR CMV.

Given the current limitations regarding the laboratory diagnosis of ganciclovir resistance, definitive laboratory confirmation of resistance generally is not available in time to guide clinical decision-making. Therefore, it is important that clinicians maintain a high index of suspicion for ganciclovir resistance in highly immunosuppressed D’R’ SOT recipients who present with clinical or virologic progression despite receipt of ganciclovir therapy. Absence of a reduction or an increase in virus load, persistence of blood culture positivity, or failure to show clinical improvement after ganciclovir has been administered intravenously twice daily for 14 days appear to be helpful in the identification of SOT recipients who have a higher likelihood of having GanR CMV as a cause of their clinical or virologic failure [17].

However, it is important to note that increases in virus load during the first 2 weeks of treatment occur frequently and are not necessarily associated with resistance, at least among stem-cell transplant recipients [38]. For SOT recipients, the precise sensitivity and specificity of these definitions are unknown and must be considered in the context of the toxicity of alternative antiviral agents. A published study has suggested that these definitions are reasonable indicators of possible ganciclovir resistance, particularly among high-risk SOT recipients, as described above [17].

### MANAGEMENT

There are no controlled studies to guide the treatment of organ transplant recipients with GanR CMV. As described in the Pathogenesis of and Risk Factors for Ganciclovir-Resistant CMV section, a variety of host and viral factors are likely to be important in determining the clinical outcome of infection with GanR CMV. The degree of ganciclovir resistance, the adequacy of the host immune response, and the severity of disease all are likely to be important in determining clinical outcome. Accordingly, interventions aimed at each of these factors are often combined in the management of patients with documented or suspected GanR CMV infection or disease. Clinical decisions regarding alternative antiviral therapy are usually based on clinical suspicion because of the delay in obtaining laboratory confirmation of resistance.

In studies published to date, most strains of GanR CMV have had mutations in UL97 alone and have not demonstrated cross-resistance to either cidofovir or foscarnet, the other antiviral agents licensed for the treatment of CMV. On occasion, however, additional mutations develop in UL54, and these mutations may confer cross-resistance to cidofovir (and, less likely, to foscarnet); however, this appears to be uncommon. Given the potential nephrotoxicity of cidofovir and the potential for
cross-resistance among ganciclovir-resistant strains, foscarnet should be considered the antiviral agent of choice for cases of suspected or documented life-threatening GanR CMV disease. Although specific data for SOT recipients are lacking, among patients with AIDS whose disease fails to respond to ganciclovir treatment for retinitis, addition of foscarnet appeared to be superior to either continuing ganciclovir or switching from ganciclovir to foscarnet monotherapy [39].

On the basis of published studies of patients with AIDS whose disease is failing to respond to ganciclovir therapy, it is reasonable to add intravenously administered foscarnet to the treatment of organ-transplant patients with severe or life-threatening suspected GanR CMV disease [39]. In addition, although no specific studies have addressed the role of CMV hyperimmune globulin in the treatment of GanR CMV, it is often administered in conjunction with a reduction in immunosuppression.

Among patients with suspected GanR CMV who are either asymptomatic or not severely ill, dosages of ganciclovir that are higher than standard dosages (up to 7.5–10 mg/kg iv b.i.d.) have been used in combination with CMV hyperimmune globulin and reduced immunosuppressive therapy. These patients have often required granulocyte colony-stimulating factor to treat the neutropenia associated with the marrow toxicity that develops with the use of such high doses of ganciclovir. If clinical disease progresses or if there is no virologic response to high-dose ganciclovir therapy, the addition of intravenously administered foscarnet may be used.

In some patients who have “nonvital” allografts (i.e., kidney) and whose illnesses have failed to respond to all other measures, immunosuppression has been discontinued, thereby sacrificing the allograft in an attempt to enhance immune recovery. Given the morbidity associated with GanR CMV infection in organ transplant recipients, controlled trials to define the optimal management of GanR CMV are clearly warranted.

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References