Cytomegalovirus Infection and Rates of Antiviral Resistance Following Intestinal and Multivisceral Transplantation

T. Ambrose[a], L.M. Sharkey[a], J. Louis-Auguste[a], C.S. Rutter[a], S. Duncan[a], S. English[b], E. Gkrania-Klotsas[c], A. Carmichael[c], J.M. Woodward[a], N. Russell[d], D. Massey[a], A. Butler[d], and S. Middleton[a,*]

Departments of [a]Gastroenterology, [b]Clinical Virology, [c]Infectious Diseases, and [d]Transplant Surgery, Addenbrooke's Hospital, Cambridge, United Kingdom

ABSTRACT

Background. Cytomegalovirus (CMV) disease is a common and clinically significant complication following intestinal or multivisceral transplantation. CMV disease is more common in cases of serologic mismatch between donor and recipient. Though in some cases it may be asymptomatic, in the immunosuppressed population it often manifests with evidence of systemic infection or end-organ disease.

Methods. We conducted a retrospective review of all patients undergoing intestinal or multivisceral transplantation over 8 years at our institution.

Results. Forty-eight transplantations were performed, with 40% of the patients (19/48) having ≥1 episode of CMV viremia, which rose to 90% in the "donor-positive, recipient-negative" (DPRN) serologic mismatch group. The median time to 1st episode following transplantation was 22.3 weeks (range, 1–78) and median duration of each episode was 4.9 weeks (range, 1.6–37.4). Six of the 19 viremic patients (31.6%) developed virologic resistance with 4 of these occurring in the DPRN group. Four of the 6 patients with drug-resistant CMV died with CMV viremia. All patients with drug resistance acquired ganciclovir resistance; these patients were more challenging to manage with second-line toxicity-limited treatments, including foscarnet, cidofovir, and leflunomide. CMV immunoglobulin has been used and we briefly discuss the use of CMV-specific adoptive T-lymphocyte transfer in the management of 1 case.

Conclusions. Post-transplantation CMV disease continues to be challenging to manage, and there is little consensus on optimal management strategies in this patient group, with a significant requirement for novel therapies; these may be pharmacologic or cell based. Extensive multidisciplinary discussion is important for most cases, but particularly for those patients who acquire virologic resistance.

IN THE United Kingdom, adult intestinal transplantation either in isolation or as part of a cluster graft including stomach, liver, and/or pancreas, is indicated for patients with irreversible intestinal failure and complications associated with parenteral nutrition (intestinal failure–associated liver disease, recurrent catheter-associated sepsis, loss of central vascular access), patients for whom extensive evisceration is required (such as with desmoid disease), and patients who require other organs but for whom survival would be compromised without inclusion of an intestinal graft [1]. Increasingly there is a need for superurgent transplantation either for liver failure associated with intestinal failure or extensive visceral ischemia, increasing the challenges of suitable tissue and infection

*Address correspondence to Dr Stephen Middleton, Department of Gastroenterology, Box 133, Addenbrooke's Hospital, Hills Road, Cambridge CB2 0QQ, United Kingdom. E-mail: stephen.middleton@addenbrookes.nhs.uk

0041-1345/16
http://dx.doi.org/10.1016/j.transproceed.2015.09.070

matching between donors and recipients. Intestinal and multivisceral transplantation are associated with numerous potential postoperative complications. Overall, infections are most common, and in the early postoperative days these are predominantly bacterial but may also be viral or fungal.

Cytomegalovirus (CMV) is the most common cause of post-transplantation viral disease; it is a beta human herpesvirus type 5 with seropositivity in the general population ranging from 30% to 90% and increasing with age [2]. Acute infection rarely causes significant clinical signs or symptoms in immunocompetent hosts but latency is established with the potential for viral reactivation. Systemic (disseminated) disease may be seen in immunocompromised patients, particularly recipients of intense immunosuppression regimens that target cellular immunity. It is a common and clinically significant infection after all types of solid organ transplantation [3–5] and is associated with increased mortality, particularly in renal and cardiothoracic transplant recipients [6,7]. CMV disease is more common in cases of serologic mismatch, especially "donor-positive, recipient-negative" (DPRN; primary post-transplantation CMV disease) [8–10]. CMV disease can manifest as asymptomatic (at least initially) CMV viremia, CMV syndrome with fever, or as end-organ disease (such as colitis/ileitis, pneumonitis, ophthalmologic complications, or meningoencephalitis, among other presentations).

We have previously reported a case of multidrug-resistant CMV infection in a patient after modified multivisceral transplantation [11]. Here we sought to review all cases of CMV disease occurring in our cohort of patients, specifically focusing on donor-recipient serology, management strategies, including novel therapies, cases of virologic resistance, and outcomes.

METHODS

We retrospectively reviewed all patients undergoing intestinal transplantation at our unit (Addenbrooke's Hospital, Cambridge University Hospitals NHS Foundation Trust, Cambridge, United Kingdom) over an 8-year period (January 2007 to December 2014) and identified those with detectable CMV viremia as measured by an in-house quantitative real-time polymerase chain reaction (PCR) assay.

Local policy defines an episode of viremia as a detectable viral load of >1,000 copies/mL for ≥10 days, following a period of ≥28 days without detectable viremia. In cases where viral load increased by >0.5 log copies/mL despite appropriate initial management (comprising reduction of immunosuppression and commencement of intravenous [IV] ganciclovir), genotypic testing for antiviral drug resistance (*Unique Long [UL] 97* and *54* genomic regions) was undertaken on plasma specimens with the use of Sanger sequencing at the national reference laboratory (Public Health England Manchester Laboratory, United Kingdom).

According to local policy, post-transplantation CMV prophylaxis was prescribed for 6–12 months to all patients who: 1) had evidence of previous exposure to CMV (were seropositive, ie, positive serum immunoglobulin G [IgG]); or 2) were seronegative (negative serum IgG) for CMV but received organs from a seropositive donor. IV ganciclovir (5 mg/kg twice daily initially, reduced to once daily after 14 days) was given for ≥14 days after transplantation and converted to oral valganciclovir (900 mg once daily, adjusted for renal function where necessary) when oral absorption was thought to be satisfactory. If patients were unable to tolerate ganciclovir or valganciclovir owing to side effects, then prophylaxis was temporarily switched to IV foscarnet (60 mg/kg once daily, adjusted where necessary for renal function). In situations where both donor and recipient were seronegative for CMV, aciclovir was given as prophylaxis against herpes simplex virus instead.

When CMV viremia was encountered, patients continued regular endoscopic surveillance for rejection in keeping with our unit's protocol; additionally all histopathologic samples underwent microscopy for CMV inclusion bodies and immunohistochemistry for CMV antigen. All CMV-viremic patients underwent regular ophthalmology review for CMV retinitis. If respiratory symptoms were present with CMV viremia, consideration was given to high-resolution computerized tomography together with bronchoscopy and bronchoalveolar lavage (BAL). BAL fluid is routinely assayed for a comprehensive panel of viral pathogens, including CMV deoxyribonucleic acid (DNA), by means of qualitative PCR.

Intravenous ganciclovir (adjusted for renal function where necessary) was used as first-line treatment for primary CMV viremia and was continued until 3 consecutive weekly plasma samples were negative for CMV DNA according to quantitative PCR or below the limit of assay detection. At that point, patients were converted back to a prophylactic dose of valganciclovir, which was continued for ≥6 months. In cases of increasing CMV viral DNA copy number in plasma according to quantitative PCR despite ganciclovir treatment, genotyping for resistant strains was carried out and patients switched to IV foscarnet (60 mg/kg 3 times daily, adjusted for renal function where necessary) as second-line therapy; significant prehydration (0.5–1 L 0.9% sodium chloride IV) is prescribed before each dose to limit renal toxicity. CMV immune globulin (Cytogam; CSL Behring) was given as an adjunct treatment to some patients, but it is not routine.

RESULTS

In the period of analysis, a total of 50 patients were transplanted, 2 of which died during surgery and were excluded from the present analysis. Two patients underwent 2 transplantations each, one because of rejection in the context of cessation of immunosuppression, and the other because of primary nonfunction of the liver graft.

Episodes of Post-transplantation CMV Viremia

Overall, 19/48 (40%) of the patients had ≥1 episode of CMV viremia (Table 1), with the highest incidence in the

Table 1. Number of Episodes of Cytomegalovirus (CMV) Viremia According to Donor/Recipient CMV Serology Status

Donor/Recipient CMV IgG Status	No of patients	Patients with CMV Episode
Negative/negative	12	0
Negative/positive	18	7 (39%)
Positive/negative	10*	9 (90%)
Positive/positive	8	3 (43%)
All patients	48	19 (40%)

*Three patients in this group required super urgent transplantation with no time to await a donor with negative CMV IgG.