Is routine post-operative surveillance for cytomegalovirus infection following heart transplantation necessary?

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Abstract

Objective: Cytomegalovirus infection (CMV) is an important cause of morbidity and mortality following cardiac transplantation. The purpose of the present study was to ascertain whether routine post-operative screening for CMV infection influenced clinical management.

Methods: Laboratory and case notes of 220 patients who received cardiac transplantation between November 1986 and October 1996 were reviewed. The range of follow-up was one to 120 (median 36) months. CMV surveillance involved blood tests for early antigen detection weekly for the first 6 post-operative weeks, fortnightly thereafter until the end of the third post-operative month and every 6 weeks to the end of the first post-operative year. Otherwise monitoring was performed if the patients had clinical symptoms suggestive of CMV infection. CMV sero-negative IgG recipients (R) of sero-positive IgG donor (D) organs and/or blood products received hyper-immune gammaglobulin for the first three post-operative months. Four patient groups were noted, namely R+D+ (59 patients), R+D− (70 patients), R−D+ (35 patients) and R−D− (56 patients).

Results: CMV antigenaemia was present in 40% (89) of patients and 48% (43) of these patients developed clinical features of CMV infection and received ganciclovir therapy. The distribution of clinical CMV infection requiring treatment was 25% (9/35) in the R+D− group, 50% (16/32) in the R+D+ group and 85% (18/22) in the R−D+ group. None of the patients in the R−D− group developed CMV antigenaemia. Forty six (52%) patients who were CMV antigen positive but who did not develop symptoms were not treated with ganciclovir and have remained well.

Conclusion: Our results suggest that routine screening for CMV following cardiac transplantation is unnecessary. Surveillance did not result in the instigation of treatment for CMV unless there were associated clinical features of CMV infection. © 1998 Elsevier Science B.V. All rights reserved

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1. Introduction

Cytomegalovirus (CMV) is the commonest opportunistic viral pathogen encountered in heart transplant recipients and is an important cause of morbidity and mortality from infection. Although it does not appear to be directly associated with acute cardiac rejection [1] the virus may be associated with the subsequent development of coronary artery disease [2]. To minimise post-operative infection it is important that CMV IgG antibody negative recipients receive CMV IgG negative donor organs and blood products whenever possible. It is important to distinguish asymptomatic from symptomatic CMV infection. Features of the latter include fever, myalgias, malaise, abdominal discomfort as well as leukopenia, pneumonitis, thrombocytopenia, atypical lymphocytosis and hepatitis [3].
The diagnosis of CMV infection is made by a combination of clinical findings, serological investigations and early antigen detection. If there is evidence of pneumonia or fibro-optic bronchoscopy is performed to obtain bronchoalveolar lavage for early antigen testing and transbronchial lung biopsy specimens for histopathological examination.

Treatment consists of intravenous ganciclovir 10 mg/kg/d (depending on renal and bone marrow function) which may be supplemented by hyper-immune globulin to CMV if necessary. CMV negative recipients of positive donor organs and/or blood products can be prescribed ganciclovir and hyper-immune gammaglobulin to CMV either singly or in combination. This may delay the onset of symptomatic CMV infection or reduce its severity.

Many cardiac transplant units perform regular post-operative serological surveillance for CMV. However, it is difficult to justify therapeutic intervention in asymptomatic patients on the basis of positive serology and antigenaemia alone. Between 1986 and 1996 our post-operative transplant protocol included routine CMV surveillance. The aim of the present study was to ascertain whether such surveillance led directly to therapeutic intervention in our patients.

2. Patients, methods and immunosuppression

Between 1986 and 1996, 286 patients received orthotopic cardiac transplantation at our unit. Sixty two patients died within the first month as a result of primary graft failure, multiple organ failure, acute rejection or infection. These patients were excluded from our follow-up data as were a further four patients in whom incomplete donor and recipient data was available. The remaining 220 patients had full pre- and post-operative virological data regarding their CMV status and post-operative infection episodes. The laboratory data and case records from these patients were retrospectively reviewed.

Our immunosuppression protocol consisted of cyclosporin-A (aiming to achieve a whole blood trough level of 500 ng/ml for the first post-operative month and thereafter 250–350 ng/ml for the first post-operative year), azathioprine 2 mg/kg/d (unless white cell count was below 4 x 10^3/l or there was significant thrombocytopenia, cholestatic liver disease or pancreatitis). Patients received 60 mg/day of prednisolone orally on the first post-operative day and this was reduced by 5 mg each day to zero. Steroids were otherwise prescribed for those patients who were intolerant of cyclosporin-A on account of renal dysfunction or for the treatment of acute rejection episodes. Forty patients received anti-thymocyte globulin (32 for induction in the early stages of the programme; eight as cytolytic therapy because renal impairment precluded early introduction of cyclosporin-A). Four patients received a 2-week course of OKT3 in the first post-operative month. CMV sero-negative recipients of positive donor organs received hyper-immune globulin, six doses, during the first three post-operative months.

Following hospital discharge patients were seen in the outpatient department and had endomyocardial biopsies performed weekly for the first 6 weeks, fortnightly for the next 6 weeks and every 6 weeks thereafter until the end of the first post-operative year. Outside of these times patients were reviewed if there was a clinical indication. In addition to endomyocardial biopsies, blood was taken for routine haematological and biochemical parameters together with cyclosporin-A level. CMV monitoring was performed using the early antigenaemia test [4]. Serological monitoring for CMV infection was by in-house and commercial enzyme immunoassays [1].

3. Results

Four recipient (R)/donor (D) patient groups were identified with respect to CMV IgG matching, namely R+D+ (59 patients) R+D− (70 patients) R+D+ (35 patients) and R−D− (56 patients). Eighty nine patients (40%) developed CMV antigenaemia post-operatively and 43 (48%) patients developed clinical evidence of systemic CMV disease and were treated successfully with intravenous ganciclovir for a two week period. Three of these patients (7%) had a period of asymptomatic CMV antigenaemia for a period of 3 weeks prior to developing systemic CMV disease. Systemic CMV infection occurred in 25% (9/35) of patients in the R+D+ group, in 50% (16/32) of the R+D− group and in 85% (18/22) of the R−D+ mismatch group. No patient in the R−D− group developed CMV antigenaemia post-operatively. Forty six (52%) patients who developed CMV antigenaemia in the absence of clinical features of CMV infection were not treated with ganciclovir and these patients have remained well.

There were 40 (19%) deaths throughout the period of follow-up. Seventeen patients (29%) died in the R+D+ group at a range of one to 93 (median 15) months following transplantation. The causes of death were sepsis in four patients, acute rejection in three patients, transplant associated coronary artery disease in three patients, carcinoma in two patients and respiratory failure, pancreatitis, renal failure, cerebral haemorrhage and lymphoma in one patient each. There were six deaths (9%) in the R+D− group at a period of 8–71 (median 33) months following transplantation. Two patients died of acute rejection and one each died as a consequence of transplant coronary artery disease and renal failure. In two patients the cause of death was not known. There were nine deaths (26%) in the R−D+ group at a range of 1–40 (median 6) months post-operatively. Three patients died of acute rejection, two from sepsis and one each from ruptured abdominal aortic aneurysm, gastro-oesophageal carcinoma and cerebro-vascular accident, for one patient the cause of death was unknown. Eight patients (14%) the R−D− group died
between one and 55 (median 5) months after transplantation. Three patients died as a result of sepsis, two from acute allograft rejection and one each as a consequence of renal failure, transplant associated coronary artery disease and systemic amyloidosis.

4. Discussion

CMV infection in immunocompromised patients can give rise to a range of complications which, in the case of interstitial pneumonitis, may be life threatening. It is because of this that many transplant centres undertake routine virological surveillance by various procedures such as serology, virus culture especially from blood, the antigenaemia test and the detection of CMV DNA or mRNA in blood using the polymerase chain reaction [1].

In our experience the decision to instigate ganciclovir therapy was based on the patients’ clinical presentation and not on laboratory data alone. We did not commence treatment for those patients with a positive IgM, greater that 4 fold increase in IgG and/or a positive antigen test unless this was also accompanied by clinical features of systemic CMV infection or pneumonitis. Although the overall mortality was higher among patients transplanted with organs from CMV positive donors, we did not observe mortality directly associated with CMV infection in our patients. However, it is appreciated that CMV may have been important in the development of transplant associated coronary artery disease. Only three (7%) patients who developed clinical evidence of systemic CMV disease had a period of asymptomatic CMV antigenaemia. Interestingly 46 (52%) of those patients with positive CMV antigenaemia did not develop clinical features of CMV infection. These patients remained well and were not treated with ganciclovir, which demonstrates that one part of this effort can be spared, this is very important in times of financial restriction. Do you think that this holds true for all kinds of patients? I mean there must be a subgroup of patients which are clinically in a very poor situation and at high risk for any event. Shouldn’t those patients at least be monitored and the others be excluded from regular monitoring?

Dr P. Thompson (London, UK): I think that the importance, as you suggest, is having a high clinical suspicion with those patients who are at risk and always having CMV as part of one’s differential for a patient who isn’t recovering as well as one might expect. I think your finding that the R-negative/D-negative patients got CMV disease, as you say, it is possible that all of these immunosuppressed patients can develop CMV disease. We just have to keep it up there in the forefront of our minds.

Dr M. Hein (Kiel, Germany): Is there any difference in the incidence of acute rejection in your 4 groups?

Dr Thompson: No, there wasn’t actually. We have looked at that, and, of course, as you suggest, there is an association between allograft rejection and CMV, but in fact in our instances the onset of rejection or the onset of CMV infection were not related.

Dr J. McCarthy (Cleveland, OH, USA): When do you begin ganciclovir? Is it just when the patient presents with symptoms? I may have been unclear on that.

Dr Thompson: Yes, we actually commence ganciclovir with the onset of symptoms. When patients have symptoms we will at that point check their rapid antigen test status. In patients who present, even more than the usual transplant patient, greater clinical concern, then we can obtain immuno-fluorescence within the same day to get that result. In the few patients there has only been five out of that group whose clinical situation was particularly poor that we actually commenced ganciclovir before we had confirmation of their CMV disease. The message is that it’s really a clinical diagnosis, and I think as clinicians looking after transplant patients, if the concern is there, it is safer in those patients to start the treatment and then get confirmation from the assays.

Dr McCarthy: I have two comments. I’m surprised in the donor-positive/recipient-negative group that you don’t commence ganciclovir empirically after the time of transplant. The second is a question really. Do you not think that CMV screening has a benefit in that it might heighten your and the patient’s awareness that there may be an impending problem.

Dr Thompson: Those are both good points. Taking your first point, the concern one has about empirically starting ganciclovir is that it has proved, certainly in our hands and in the hands of most units, very effective at treating CMV disease, but our concerns are over CMV resistance. Fortunately we haven’t had that at St. George’s yet and hopefully we won’t see it. So we are rather concerned about just starting it empirically, though I accept that a high percentage of that population do end up requiring ganciclovir due to symptoms. All of our patients, we have a high suspicion of any symptoms that they present with, so they are all given a heightened...
awareness. I think the point you make about us clinicians, that it heightens our awareness that there may be a problem coming on, that is fair, but I think it’s debatable as to whether we should just be thinking about it anyway. It is one of the significant problems that we get post-transplantation. It should always be in the forefront of our minds. I’m not necessarily convinced that we need to have a rapid antigen test result in the notes to confirm that we’re thinking of it.