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Preemptive Strategy for Cytomegalovirus (CMV) Disease Prevention in High Risk (D+/R-) Liver Transplant Recipients Receiving Induction Therapy: Effective But Not Optimal

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Abstract

Background:
Guidelines recommend 3-6 months of valganciclovir for CMV disease prevention in high risk (CMV IgG D+/R-) organ transplant recipients, though a pre-emptive strategy is an alternative. The liver transplant (LT) program at Cleveland Clinic uses 2 weeks of prophylaxis followed by a pre-emptive protocol. We sought to assess the efficacy of this strategy.

Methods:
For CMV IgG D+/R- LT recipients from 4/09-4/12, we retrospectively collected baseline and clinical data for 6 months from LT. Primary outcomes were symptomatic CMV infection and disease and CMV viremia. Secondary outcomes included patient and allograft survival, rejection, CMV occurrences, viral loads, hospitalizations and CMV resistance.

Results:
Of 69 D+/R- LT recipients, 58 received induction (9 rATG, 49 basiliximab). Symptomatic CMV infection or disease occurred in 14/69 (20%), 12/58 with induction and 2/11 without. CMV viremia occurred in 45/58 (77.6%) with induction vs. 5/11 (45.4%) without (P= 0.06). All 9 with rATG developed viremia. Analyses of secondary outcomes by induction vs. no induction were not statistically significant. 5/9 (55.6%) with rATG required IV therapy or hospitalization compared to 16/49 (32.7%) with basiliximab. Median initial and peak viral loads were higher with rATG than basiliximab, log 3.33 c/ml (IQR 3.07- 4.17) vs. 2.9 (IQR 2.72- 3.3) (P= 0.005), and log 4.28 c/ml (IQR 3.47- 4.69) vs. 3.7 (IQR 3.34- 4.08) (P< 0.05). Mean CMV occurrences were greater with rATG than basiliximab or no induction at 2.11, 1.18 and 0.73, respectively (P= 0.008). Time to CMV infection was statistically significant between patients with induction and those without.

Conclusion:
A pre-emptive strategy was reasonably effective at preventing invasive CMV disease and early indirect effects in CMV D+/R- LT recipients. However, this approach does not appear optimal, as evidenced by high rates of CMV infection, many requiring IV therapy or hospitalization, and frequent recurrences.

Introduction

Direct and indirect effects of CMV infection have affect morbidity and mortality following organ transplantation. Risk factors for CMV infection after transplantation include CMV D+/R- and use of lymphocyte depleting antibodies (1, 2).

Guidelines recommend CMV prophylaxis with valganciclovir for 3-6 months in high risk organ transplant recipients, recognizing limitations to valganciclovir prophylaxis in LT recipients (3). An alternative pre-emptive strategy of monitoring for CMV viremia with early antiviral therapy is also advocated (3,4). The liver transplant program at CCF uses a largely preemptive strategy with 2 weeks of prophylaxis followed by weekly preemptive monitoring for 12 months.

Patients and Methods

Patients >18 years of age receiving a liver transplant only from 4/09 to 4/12 at the Cleveland Clinic CMV IgG D+/R- were included. Those that died within 2 weeks of LT were excluded.

The immunosuppression protocol: tacrolimus, mycophenolate mofetil, and prednisone. Induction was decided on a case basis. Those on hemodialysis prior to LT received rATG with tacrolimus delayed until POD 10. Patients with hepatocellular carcinoma, positive cross- match, or creatinine >1.5 mg/ dL received basiliximab. No induction was given if creatinine was <1.5 mg/ dL.

CMV prevention protocol: CMV D+/R- received ganciclovir at 5 mg/kg Q 12 or valganciclovir 900 mg bid for 14 days, then acyclovir 400 mg bid for 6 months. CMV DNA was monitored weekly for 12 months by PCR whole blood assay. If viral replication was detected, antiviral therapy was initiated.

Data for 6 months following the date of transplant was collected by retrospective chart review and analyzed using Excel (Microsoft) and JMP (SAS). The primary outcome was CMV infection, stratified by asymptomatic DNAemia, symptomatic infection (defined as fever, GI symptoms, malaise, or leukopenia), and biopsy- proven tissue- invasive disease. Secondary outcomes included patient and allograft survival, allograft rejection, number of CMV occurrences, peak viral loads, need for hospitalization, and development of CMV resistance.

Results

69 D+/R- patients were identified, 58 of whom received induction therapy. 49 patients received basiliximab and 9 received rATG; 2 patients received both basiliximab and rATG and were included in the rATG group for statistical analysis. 14/69 (20%) patients developed symptomatic CMV disease, 12/59 (20%) in the group who received induction and 2/11 (18%) in the group that did not; differences were not statistically significant (Table 1). Two patients developed tissue-invasive CMV disease, both in the group that received induction; one received rATG only, and the other received basiliximab only. CMV infection occurred in 45/58 (77.6%) of patients who received induction vs 5/11 patients (45.4%) who did not receive induction (P= 0.06). All 9 patients who received rATG developed CMV infection. There were no cases of rejection following CMV disease during 6 month follow- up. Two deaths occurred in the follow- up interval, neither of which were attributed to CMV. Analyses of secondary outcomes by induction regimen were not statistically significant.

Table 1: Outcomes

	No Induction (N=11)	Basiliximab (N=49**)	rATG (N=9)
CMV symptoms*	2 (18.18%)	13 (26.53%)	2 (22.22%)
Biopsy- proven CMV	0	1 (2.04%)	1 (11.1%)
CMV resistance	0	1 (2.04%)	1 (11.1%)
IV Therapy	2 (18.18%)	16 (32.65%)	5 (55.56%)
Hospitalization	2 (18.18%)	16 (32.65%)	5 (55.56%)
Median log initial viral load	3.01	2.9	3.33
Median log peak viral load	3.72	3.702	4.27
Death or allograft loss	0	2 (5.56%)	0
Rejection after CMV infection	0	0	0

Symptoms: fever, malaise, GI symptoms, leukopenia
**** Total N of basiliximab 51; 2 people received both rATG and basiliximab and are included with the rATG group for statistical analysis.**

Median initial and peak viral loads were higher in patients who received rATG than patients who had received basiliximab, log 3.33 c/ml (IQR 3.07- 4.17) vs. 2.9 (IQR 2.72- 3.3) (P= 0.005), and log 4.28 c/ml (IQR 3.47- 4.69) vs. 3.7 (IQR 3.34- 4.08) (P< 0.05). Mean CMV occurrences were greater with rATG than basiliximab or no induction at 2.11, 1.18 and 0.73, respectively (P= 0.008) (Figure 1). Time to CMV infection was statistically significant between patients with induction and those without (Figure 2).

Figure 1. Mean CMV occurrences

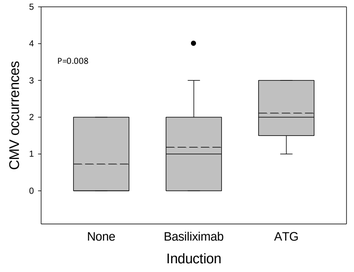
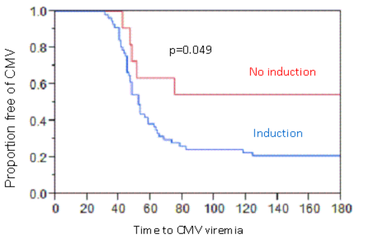


Figure 2. CMV- free survival



Conclusions

•Preemptive strategy was reasonably effective in preventing symptomatic and invasive CMV disease in CMV D+/R- LT recipients at 6 months follow up

•Greater rates of CMV infection and higher viral loads in patients receiving lymphocyte- depleting induction therapy warrants reconsideration of antiviral prophylaxis in this group

•Numbers were small, but the potential CMV resistance in the rATG group warrants further attention

•Single center study limited by relatively small sample size and limited follow up

References

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