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Cut-Off of CMV Cobas® Taqman® (CAP/CTM Roche®) for Introduction of Ganciclovir Pre-Emptive Therapy in Allogeneic Hematopoietic Stem Cell Transplant Recipients

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Abstract : Background: The introduction of prophylactic or preemptive therapies has effectively decreased the CMV mortality rates after hematopoietic stem cell transplantation (HSCT). CMV antigenemia (pp65) or quantitative PCR are methods currently approved for CMV surveillance in pre-emptive strategies. Commercial assays are preferred as cut-off levels defined by in-house assays may vary among different protocols and in general show low reproducibility. Moreover, comparison of published data among different centers is only possible if international standards of quantification are included in the assays. Recently, the World Health Organization (WHO) established the first international standard for CMV detection. The real time PCR COBAS Ampliprep/ CobasTaqMan (CAP/CTM) (Roche®) was developed using the WHO standard for CMV quantification. However, the cut-off for the introduction of antiviral has not been determined yet. Methods: We conducted a retrospective study to determine: 1) the sensitivity and specificity of the new CMV CAP/CTM test in comparison with pp65 antigenemia to detect episodes of CMV infection/reactivation, and 2) the cut-off of viral load for introduction of ganciclovir (GCV). Pp65 antigenemia was performed and the corresponding plasma samples were stored at -20°C for further CMV detection by CAP/CTM. Comparison of tests was performed by kappa index. The appearance of positive antigenemia was considered the state variable to determine the cut-off of CMV viral load by ROC curve. Statistical analysis was performed using SPSS software version 19 (SPSS, Chicago, IL, USA.). Results: Thirty-eight patients were included and followed from August 2014 through May 2015. The antigenemia test detected 53 episodes of CMV infection in 34 patients (89.5%), while CAP/CTM detected 37 episodes in 33 patients (86.8%). AG and PCR results were compared in 431 samples and Kappa index was 30.9%. The median time for first AG detection was 42 (28-140) days, while CAP/CTM detected at a median of 7 days earlier (34 days, ranging from 7 to 110 days). The optimum cut-off value of CMV DNA was 34.25 IU/mL to detect positive antigenemia with 88.2% of sensibility, 100% of specificity and AUC of 0.91. This cut-off value is below the limit of detection and quantification of the equipment which is 56 IU/mL. According to CMV recurrence definition, 16 episodes of CMV recurrence were detected by antigenemia (47.1%) and 4 (12.1%) by CAP/CTM. The duration of viremia as detected by antigenemia was shorter (60.5% of the episodes lasted ≤ 7 days) in comparison to CAP/CTM (57.9% of the episodes lasting 15 days or more). This data suggests that the use of antigenemia to define the duration of GCV therapy might prompt early interruption of antiviral, which may favor CMV reactivation. The CAP/CTM PCR could possibly provide a safer information concerning the duration of GCV therapy. As prolonged treatment may increase the risk of toxicity, this hypothesis should be confirmed in prospective trials. Conclusions: Even though CAP/CTM by ROCHE showed great qualitative correlation with the antigenemia technique, the fully automated CAP/CTM did not demonstrate increased sensitivity. The cut-off value below the limit of detection and quantification may result in delayed introduction of pre-emptive therapy.

Keywords : antigenemia, CMV COBAS/TAQMAN, cytomegalovirus, antiviral cut-off
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