Rukiye Taskin

Dr. med.

“Biomarkers in Heart Transplantation”

Promotionsfach: Innere Medizin

Doktorvater: Prof. Dr. med. T. J. Dengler

The prognosis of heart transplant patients has increased over the last years. The one-year survival rate is over 80 % [2,1]. However, acute rejection as well as transplant vasculopathy (TVP) are still serious problems. Beside cancer accelerated transplant vasculopathy (TVP) still limits the long-term survival after heart transplantation. Although major improvements have been made in the prevention and treatment of acute transplant rejection, accelerated TVP or cancer still limits the long-term success of heart transplantation (HTx). Unfortunately there are no reliable and easily available parameters for routine noninvasive rejection monitoring after heart transplantation, none of them has the potential to replace EMB as the gold standard. No simple prognostic indicators have yet been described for first year mortality and TVP. This study was aimed at testing biomarkers, such as Gal-3BP, Osteopontin, IL-17, LIGHT and hsTNT to develop biomarkers with predictive, diagnostic and prognostic applications in heart transplantation.

This study provides evidence that the presence of serum Gal-3BP level is related to adverse outcome after heart transplantation. The results clearly demonstrate that in cross-sectional and longitudinal analysis the presence of elevated serum Gal-3BP levels in the sera of heart transplant recipients were predictive for the major complication TVP ($p<0.0001$). In addition, higher levels of Gal-3BP serum levels after transplantation are also a predictor for first year mortality after heart transplantation. Moreover, a prominent downregulation of serum Gal-3BP levels are associated with mortality within the first year after heart transplantation ($p=0.02$). Furthermore, serum Gal-3BP as well as local mRNA expression levels are associated with cellular rejection episodes in patients without a TVP (both $p=0.01$). In conclusion, the results of our study clearly show that serum Gal-3BP seems to be a potent

biomarker of predicting TVP in cardiac allograft recipients and a prognostic marker for first year mortality.

Interestingly, our results show a time-dependent decrease in the OPN serum levels in transplanted patients, where OPN serum levels of transplanted patients need more than 5 years to reach the median level of healthy patients. Our finding indicates the prolonged remodeling process. It can lead to speculation whether OPN might be useful biomarker of remodeling. More remarkably the remodelling process is not associated with the diagnosis of TVP. Our data demonstrated that the serum OPN level may not provide clinically helpful information for the evaluation of an acute rejection.

On the basis of our data, it can be assumed, that there might be a relationship between increasing OPN levels and risk of death. It is important to realize, that transplanted patients with early death have significantly higher serum OPN levels than patients with long-survival. This supports the idea that increases in OPN serum levels are associated with poor survival.

Our results show that the expression of LIGHT and IL-17 serum level is not associated with the presence of TVP. We found an increase in the median LIGHT serum level during the acute rejection ($p=0.01$). No significant differences were observed in the median IL-17 levels pre rejection, during the acute rejection and post rejection. LIGHT and IL-17 provide no prognostic information for death within the first year after heart transplantation and TVP.

hsTNT serum levels showed a strong association to cardiac allograft recipients who died within the first year compared to long term survivals after HTx ($p=0.001$). In addition, serum levels of hsTNT were significantly increased during a follow-up period of 5 years in patients with a TVP compared to cardiac recipients without a TVP (all $p<0.05$). Interestingly, there was no association between hsTNT levels and the acute rejection period. Heart transplanted patients with hsTNT serum levels above 14ng/L had a significantly increase in transplant vasculopathy and higher NT-BNP levels ($p=0.04$ and $p=0.02$). In conclusion the study provides the observations that hsTNT was detectable in almost all our patients. The hsTNT assay provides a strong prognostic information for death of any cause within the first year after heart transplantation and for TVP in cardiac allograft recipients. In contrast, hsTNT was not associated with the incidence of histological acute rejection.