Abstract: **P510**

**Anthracycline cardiotoxicity 2.4 or Toll-Like Receptor root of all evil**

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**Background/Introduction**
Recent studies have shown that TLR receptors (that recognize the "vital" structural components of microbes, stable evolutionary components) are activated by endogenous signals, such as heat shock proteins and oxidative stress, which can contribute to congestive heart failure. These receptors mediate the release of mediators, initiating the inflammatory response and paving the way for immune-enhanced immune-strength forces.

**Purpose**
The purpose of this study is to assess the role of TLR2 and TLR 4 gene expression as an early marker for the risk of doxorubicin induced cardiomyopathy in correlation with early diastolic dysfunction in patients treated with doxorubicin. Thus, we hypothesized that TLR receptors contribute to the pathogenesis of Doxorubicin-induced cardiac dysfunction through an inflammatory mediated mechanism.

**Methods**
Our study included 50 consecutive patients who received doxorubicin therapy for a wide range of oncological and haematological pathology (lymphomas, leukaemia, multiple myeloma, breast cancer etc.), aged 18-70 years, with a >6 months survival probability and with a left ventricular ejection fraction (EF) >50%.

The exclusion criteria in the study were: previous anthracycline therapy, previous radiotherapy, history of heart failure or chronic renal failure, atrial fibrillation, and pregnancy.

Gene expression was assessed by quantitative reverse transcription PCR (qRT-PCR) using blood collection, RNA isolation, cDNA reverse transcription, qRT-PCR and quantification of the relative expression. At enrolment in the study, all patients were evaluated clinically and ECG and echocardiography was performed (for diastolic performance). Left ventricular (LV) diastolic performance included early (E) to late (A) ventricular filling velocities, where E:A ratio is a first generation test for diastolic performance of the heart. At 6 months (6M) a follow-up of patients was performed.

**Results**
The average global amount of gene expression units (initial determination + follow-up) was 0.128 for TLR4 (range 0.048-0.824) and 0.238 for TLR2 (range 0.021-0.287). The mean mRNA extracted quantity was 119,334 \(\mu\)g/\(\mu\)l.
As for the diastolic function parameters, criteria for diastolic dysfunction were present after 6 months in 31 patients (62%). For these patients, with diastolic dysfunction, the mean values for TLR4 were 0.1198625 and for TLR2 0.16454 gene expression units. In the entire 6M follow up patients group the mean value for TLR2 was 0.31 ± 0.17 and for TLR4 0.16 ± 0.02. The corresponding values for the patients who did not developed diastolic dysfunction were 0.14 ± 0.05 for TLR2 (p = 0.01) and 0.14 ± 0.11 for TLR4 (p=0.2).

Conclusions

Our study suggests that TLR4 and TLR2 expression is higher in patients under doxorubicin therapy which develop diastolic dysfunction. This may suggest a predisposition to myocardial involvement, a higher sensitivity to doxorubicin cardiac effects.