Serum amino-terminal pro-brain natriuretic peptide in hematological patients with neutropenic fever: a prospective comparison with C-reactive protein

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INTRODUCTION
- According to some studies serum aminoterminal pro-brain natriuretic peptide (NT-proBNP) is considered to be a prognostic predictor in severe sepsis.
- No data are available on NT-proBNP kinetics in hematological patients with neutropenic fever.

AIMS OF THE STUDY
- To evaluate the kinetics of NT-proBNP and CRP in hematological patients with neutropenic fever.
- To evaluate NT-proBNP and CRP as early indicators of severe sepsis.

PATIENTS AND METHODS
- The study population consisted of 44 males and 26 females with a median age of 56 (range 18-70) years with neutropenic fever. There were 19 AML patients and 51 ASCT recipients (25 no n-Hodgkin lymphoma, 14 multiple myeloma, 9 Hodgkin lymphoma, 2 chronic lymphocytic leukaemia and 1 AL-amyloidosis).
- Periods with neutropenic fever were divided to those complicated by severe sepsis and those not complicated by severe sepsis. The first samples for measurement of NT-proBNP and CRP were taken at the beginning of neutropenic fever (>38°C) (d0) and then daily for 3 to 4 days.
- Samples for NT-proBNP measurement were drawn by venipunctures from patients lying in supine position to lithium heparin-containing tubes. Plasma was separated and NT-proBNP was determined within 24 hours using electrochemiluminescence immunoassay (ECLIA, Roche Diagnostics) on a Cobas e 601 analyzer (Hitachi High Technology Co, Tokyo, Japan).
- Ten patients had previous cardiovascular disease (2 hypertension and coronary heart disease, 2 hypertension and chronic atrial fibrillation, 2 previous coronary by-pass, 2 cardiomyopathy, 2 mixed type cardiomyopathy, 1 hypertension and aortic valve sclerosis). Altogether 20 (29%) patients received ACE-inhibitors, 13 (19%) beta-blockers, and 17 (24%) diuretics.
- The analyses were performed with SPSS version 14.0 for Windows (SPSS, Inc. Chicago, IL, USA). To correct the skewed distribution of NT-proBNP and CRP, a logarithmic transformation was used. After logarithmic transformation a near-normal distribution was achieved for NT-proBNP and CRP. Analysis of variance (ANOVA) for repeated measurement was used to evaluate possible differences between subgroups in NT-proBNP and CRP levels in repeated measurements during days 0-3. A p-value < 0.05 was considered significant.

RESULTS
- The diagnostic criteria for severe sepsis were fulfilled in 13/ 4 neutropenic fever periods (14%). The median time after the onset of fever to the point when the criteria for severe sepsis were fulfilled was 1 day (range 1-7).
- CRP maximum was achieved on day 2 and NT-proBNP on day 4 (Figure 1).
- There were no statistically significant differences between the subgroups with and without severe sepsis in the level of NT-proBNP at any time point (Figure 2). After excluding subjects with previous cardiovascular disease the finding remained similar.
- Two patients (15% of the patients with severe sepsis) died due to septic shock in intensive care unit; one ASCT recipient after one day of admission and one after second laparotomy because of appendicitis while still neutropenic after the second induction treatment for AML.
- The levels of NT-proBNP were higher in the subgroup of previous cardiovascular disease than in the subgroups without previous cardiovascular disease throughout the course of the neutropenic fever (Figure 3).

CONCLUSIONS
- In this single centre prospective study neither serial NT-proBNP nor CRP could predict the development of severe sepsis in patients with neutropenic fever.
- There were no significant differences in the levels of NT-proBNP between patients with and without severe sepsis at any time point.
- Slow increase of NT-proBNP lasted through the whole study period from day 0 to day 4, whereas the highest median value of CRP was reached on day 2.
- Taking into account that the median time to fulfilment of criteria for severe sepsis was only one day it is obvious that NT-proBNP cannot be used as an early marker of severe sepsis in patients with neutropenic fever. NT-proBNP in neutropenic fever rather seems to be a marker of previous cardiovascular disease and cardiovascular stress associated with sepsis.