The Results of the Russian Clinical Trial of Mesenchymal Stromal Cells (MSCs) in Severe Neutropenic Patients (pts) with Septic Shock (SS) (RUMCESS trial)

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Abstract

Background: Recent evidence suggests that MSCs might improve survival during sepsis in animal models. However, no study has investigated the effects of MSC therapy on the survival of pts with sepsis and SS, especially severe-neutropenic pts.

Aim: The aim of this study was to investigate the efficacy of the administration of MSCs for the treatment of SS in neutropenic pts.

Patients and Methods: This prospective, single-center, randomized Russian clinical trial of MSCs in severe neutropenic pts with SS (RUMCESS) (NCT 01849237) was approved by the local ethics committee and was begun in December 2012. Neutropenic pts (WBC < 0.5x109/l) with SS were enrolled on to the study. The pts were randomly assigned (1:1) to receive either conventional therapy (CT) of SS (CT group), or CT plus donor MSCs at a dose of 106/kg intravenously within the first 10 hours after SS onset (CT+MSCs group). Written informed consent was obtained for all pts. All pts were admitted and treated in the ICU of the National Research Center for Hematology (Moscow). The Acute Physiology and Chronic Health Evaluation (APACHE) II score and Sepsis-related Organ Failure Assessment (SOFA) score were employed to determine the severity of illness. Pts were followed up for 28 days after enrolment in the study, and 28-day all-cause mortality was assessed.

Pts characteristics and complication rates were compared using Fisher's exact test. The Kaplan-Meier method with the log-rank test, and Cox proportional hazard regression model were used to determine the statistical significance of the relationship between overall survival (OS) and the treatment regimen. Statistical analyses were performed using SAS 9.1.

Results: Of the 27 neutropenic pts with SS, 13 received CT and 14 received CT+MSCs. There were no statistically significant differences in the demographic variables between groups . The CT group included 7 males, 6 females, aged 33-81 yrs, median 55 yrs. The CT+MSCs group included 6 males, 8 females, aged 30-75 yrs, median 48 yrs. Hematological disorders were also similar in the two groups: AML (4), NHL (4), HL (1), MM (3), MDS (1) in the CT group, and AML (5), NHL (7), MM (1) in the CT+MSCs group. In all pts, except for one with MDS, neutropenia developed after chemotherapy. In 8/13 pts in the CT group and 9/14 pts in the CT+MSCs group blood cultures were found positive, mostly gram-negative. Baseline APACHE II scores (34.2 [95% CI 28.3-43.1] and 32.2 [95% CI 26.2-37.5] in the CT- and CT+MSC-groups, respectively), and SOFA scores (17.9 [95% CI 13.5-22.2] and 15.1 [95% CI 11.0-19.2] respectively), were similar in the two groups. 28-day survival rates were 15% (2 out of 13 pts) in the CT group and 57% (8 out of 14 pts) in the CT+MSCs group (P=0.04) (Figure 1). The

significant increase in 28 days OS of the pts in CT+MCSs group was associated with SOFA score decrease, which was started in three days after onset of SS. Despite higher 28-day survival rates only 3 pts treated with CT+MSCs remained alive after 3 months, and 5 of 8 pts from the CT+MSCs-group who survived 28 days died later because of sepsis-related organ dysfunction.

Conclusions: Administration of MSCs in the first hours of SS might improve short-term survival in neutropenic pts, but does not prevent death from sepsis-related organ dysfunction in the long term. Perhaps repeated administration of MSC is required.

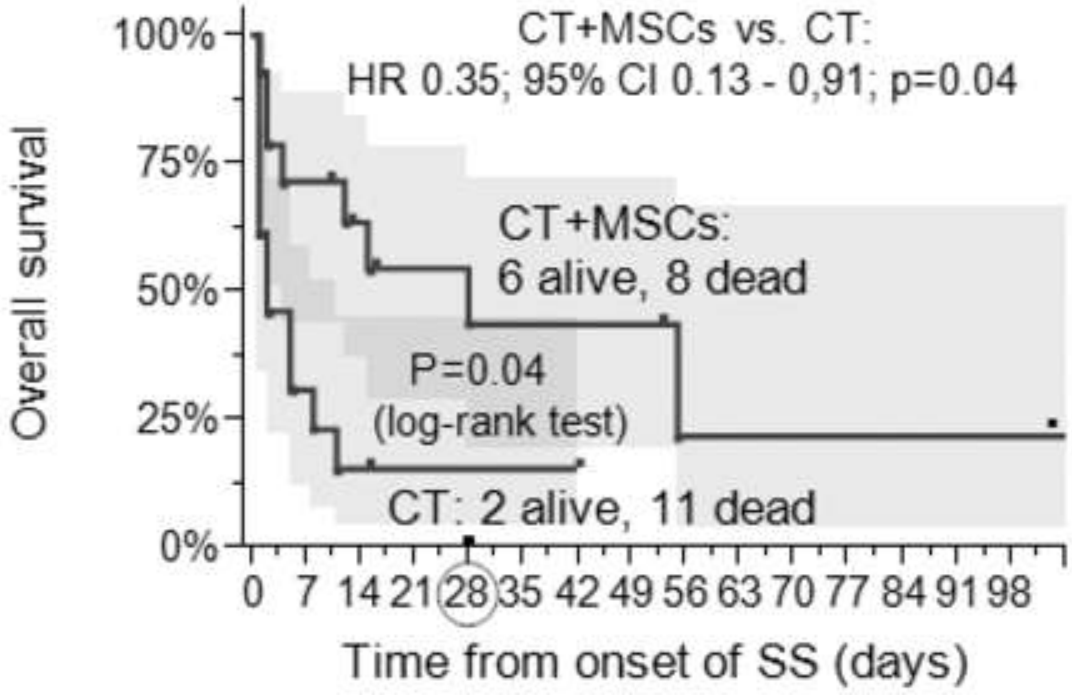

Figure 1.

Comparison of OS rates between the two groups of pts in the ICU. There was a statistically significant increase of the 28-day OS rates (42% vs. 15%; P=0.04) and a statistically significant decrease of the risk of death (HR 0.35; 95% CI 0.13 - 0.91; P=0.04) in the CT+MCSs group vs. the CT group.