Summary:

In this thesis section “Oral Mucositis (OM) and oral Graft versus Host Disease (GVHD) in patients after allogeneic stem cells transplantation and with focus to FLU/MEL conditioning regimen” the author deals with following issues:

1. Literature overview: The overall negative impact of OM is mentioned and the complex pathogenesis, clinical characteristics, incidence and factors influencing both OM and GVHD are described. The histological features of GVHD and classification of it are mentioned, too. Conventional and reducedintensity conditioning transplant regimens, including FLU/MEL are presented.

2. Methodological section: Prospective observational study of 117 patients after allogeneic stem cells transplantation with BU/CY2/±ATG (26%), FLU/MEL (60%), FLU/CY (9%), Bu/FLU/ATG (2%) and HD-CY/ATG (2%) conditioning regimens. OM assed according to WHO criteria, GVHD assessed according to NIH criteria accepted by the EBMT. The statistical univariate analysis performed by means of GraphPad In Stat - Statistica Software (Man-Whitney, Fisher, t-test), $p<0,05$ considered significant. Multivariate analysis used in OM risk factors assessment.

3. Results: The OM incidence was significantly dependent on pre-transplant conditioning regimen (Bu/CY2/±ATG: 100%, FLU/MEL: 78%, FLU/CY: 9%, $p=0,0001$) in multivariable analysis. OM kinetics and severe OM (gr.3-4 WHO) were comparable in FLU/MEL vs. Bu/CY2/±ATG. In FLU/MEL patients, OM more often observed in women compared to men (89% vs. 67%, $p=0,04$) and in patients with lower body mass index (26 (14-39) vs. 28 (17-43), $p=0,01$). Incidence of acute GVHD was significantly higher in patients with OM persisting over day +21 post-transplant (68% vs. 32%, $p=0,005$) and logistic regression proved significant dependence of acute GVHD on severity and duration of OM ($p=0,04$). In FLU/MEL, acute oral GVHD was observed in 8%

of patients with onset in median of day 85 (40-140) post-transplant and with duration of 24 (7-54) days, the bucal mucosa was affected in 100% and lichenoid changes observed in 83% patients. In FLU/MEL, chronic oral GVHD was observed in 29% of patients with onset in median of day 230 (107-540) post-transplant and with duration of 133 (7-54) days, the bucal mucosa was affected in 100% and lichenoid changes observed in 100% patients. In 14/27 FLU/MEL patients histology of bucal mucosa presenting clinically with lichenoid features (4 cases acute and 8 chronic GVHD) was analyzed, in 100% samples the apoptotic bodies and interface inflammation was observed. No specific characteristic features were found in acute and chronic GVHD.

4. Conclusions: Characteristics of OM and oral GVHD were analyzed in patients after allogeneic stem cells transplantation and the FLU/MEL conditioning regimen was in focus. The FLU/MEL and BU/CY2/±ATG posses high oral-toxicity potential, contrary to FLU/CY. Severe oral GVHD is rare in FLU/MEL patients, however, with respect to long-time duration of the complication this can be considered as clinically significant problem. It can be complicated to distinguish acute and chronic GVHD if not assessed in holistic clinical context – morphological and histological features are similar in both forms of GVHD. Lichenoid changes were observed both in acute and chronic oral GVHD in this cohort of patients, which stays in contrast to literature data where lichenoid changes are considered significant for chronic GHVD. Curiously, literature describing oral GVHD features is remarkably rare.

Kaposi´s sarcoma after allogeneic peripheral stem cell transplantation – rare secondary neoplasia.

The iatrogenic subtype of Kaposi´s sarcoma (KS) is predominantly observed in renal transplant patients. Its occurrence after stem cell transplantation is extremely rare. In a 58-year-old woman with B-ALL, the KS had developed in the period of days +90-120 after sibling donor allogeneic peripheral stem cell transplantation. The KS presented as multitude 3-5mm papules of dark blue, purplish color. Histologically, haphazardly oriented fascicles of spindled cells separated by irregular vascular lumina or slit-like vessels and rare hyaline PAS-positive globules were identified. HHV-8 DNA sequences were detected by PCR-primers KSHV-1 a KSHV-2. The onset of KS in the patient correlated with CMV reactivations, suggesting that perhaps CMV infections could aggravate it. Treatment with ganciclovir and foscavir did not resulted in KS regression. The KS spontaneously and gradually regressed within days +270-390 post-transplant, when no CMV or any other clinically important infection was evident, and immunosuppressive treatment was reduced. Further observations of KS and HHV-8 after organ transplantation are necessary to help understand the nature of this complication.