Relevance of tumor infiltrating lymphocytes as a prognostic factors in patients with portal vein embolisation (PVE) and patients with PVE and administration of autologous stem cells

Background: low future liver remnant volume (FLRV) is the cause of why 75% of patients with colorectal liver metastases (CLM) are primarily inoperable. Portal vein embolisation (PVE) helps to increase FLRV and so increase the operability. But PVE fails in almost 40 % of patients. Usage of stem cells (SCs) could be the way how to support the effect of PVE. Currently, there are studies of interactions of the immune system and malignancies. We do not know about papers focused on relations of the immune system and CLM in patients treated by PVE. There were not described interactions of ABC transporters and CLM at patients after PVE was performed too.
Aims: the aim of this dissertation was to verify the effect of PVE and intraportal administration of SCs on the growth of FLRV and progression of the CLM. Other aims were to evaluate the tumor infiltrating lymphocytes, ABCC10 and ABCC11 transportes in patients treated by surgery for CLM after PVE and their clinical relevances.
Methods: intraportal administration of SCs after PVE and their effect was explored in a group of 63 patients (43 patients with PVE alone, 20 in the group PVE with SCs). FLRV and volume of CLM were assessed from CT scans. Their growth was observed also in relation with resectability, disease free interval (DFI) and overal survival (OS). The cohort of 101 patients was used for assessement of tumor infiltrating lymphocytes (PVE 26 patients, PVE and SCs 13 patients, 62 patients with primarily resectable CLM). We assessed numbers and localization of TILs – peritumoral (PTL), intratumoral (ITL), intrastromal (ISL) and Crohn like infiltration were assessed. Imunohistological staining for $CD4^+$,$CD8^+$,$CD25^+$ and $FoxP3^+$ lymphocytes (TILs) and for $CD57^+$ and $CD86^+$ cells and Granzym B was used. Serpin B was assessed in the cancer cells. The ratio between TILs was also focused. Histological and microscopical examination for ABCC10 and ABCC11 transporters was performed in 86 patients (23 with PVE, 13 with PVE and SCs and 54 with primarily resectable)
Results: study did not prove significant acceleration of FLRV growth after SCs administration. The fastest growth was observed in patients with initial FLRV lower than 30 %. Growth of VLM was not accelerated. Patients with administered SCs had lower number of explorative laparotomies and extrahepatal metastases during follow up. OS after resection was comparable to patients with PVE and primarily resected. The TILs assessement did not prove activation of cytotoxic reaction. Patients with PVE had higher levels of regulatory T cells lymphocytes ($CD25^+$, $FoxP3^+$) (T reg). We observed lower levels of CD4+ in the patients with PVE and SCs administration. The diferences were also observed in ITL, ISL and Crohn like infiltration. $CD4^+$ PTL infiltration was lower in all patients with PVE. High infiltration of $CD4^+$ and ISL infiltration were connected with early recurrency of the disease in all patients with PVE. TILs ratio showed higher infiltration of maturated T reg in all patients with PVE. Higher ratio FoxP3/CD25 decreased risk of recurrency in all resected patients. CD8/CD4 was a negative prognostic factor of the primarily resectable patients, because increasing ratio decreased DFI. Assessement of ABCC10 and ABCC11 did not prove significant diferences between observed groups.
Conclusion: PVE is beneficial for patients with primarily unresectable CLM. Patients with intraportal administration of SCs had lower number of exploratory laparotomies and extrahepatal metastases during follow up. The cause of this situation would be the object of further research. Study did not prove activation of cytotoxic immunity at CLM. T reg could be a supporting factor for liver atrophy in the liver lobe, where the occlusion of the portal vein was performed. Higher ratio FoxP3/CD25 was a positive prognostic factor that increased DFI in patients with liver resection for CLM.

Key words: colorectal cancer, liver metastases, portal vein embolization, future liver remnant volume, stem cells, tumor infiltrating lymphocytes, ABCC transporters