Targeting the Graft-Versus-Tumor Effect of DLI by Regional Hyperthermia to the Tumor Compartment.

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Introduction:

Donor lymphocyte infusion (DLI) in combination with chemotherapy and regional hyperthermia (RHT) was used to target graft-versus-tumor (GvT) effect to the tumor compartment in a patient with recurrent alveolar rhabdomyosarcoma (aRMS).

Patients and methods:

A 15-year old girl was diagnosed with stage IV aRMS in the left nasal cavity with bone marrow infiltration. She received standard chemotherapy and concurrent hyperfractionated radiotherapy of the primary tumor region according to the high-risk arm of the CWS-IV 2002 protocol for the treatment of soft tissue sarcoma. Remission was consolidated applying double high dose chemotherapy with autologous stem cell rescue followed by haploidentical stem cell transplantation from the father in first complete remission, based on the Meta-EICESS-protocol for multifocal Ewing tumor. 11 months after haploidentical SCT, control scans showed no evidence of disease and complete donor chimerism was confirmed. 17 month after SCT however relapse of the aRMS in the pancreas was diagnosed by PET-CT and confirmed histologically. In order to enhance the graft versus tumor effect, DLI were applied preceded by reduced ICE chemotherapy (50-75% dose reduction) combined with RHT to the relapse site. Reduced ICE was given for regulatory T cell depletion before DLI. RHT was given for regional targeting of DLI. 12 cycles of reduced ICE and RHT were preformed combined in total with two donor lymphocyte infusions from the patient's father.

Results:

After the patient received DLI and the first cycle of the combined therapy graft versus host disease (GvHD) of the skin developed and the patient's clinical condition improved. After the second DLI PET-CT showed significant tumor regression. During this period of time the amount of CD94+CD56bright and CD16dim NK cells was elevated. Cytotoxicity as determined in a Europium assay against K562 cells was found to be elevated. 9 months after the first DLI/RHT the patient died due to tumor progression. In vitro results showed a higher frequency of undifferentiated NK cells, which increased during disease progression. In particular, strong reduction in the percentage of CD56+CD16+ NK cells and an increase in NKG2D negative NK cells was observed during progression. The CD94+ NK cell subset was enriched throughout the observation time with slight increase as disease progressed and cytotoxic molecules and degranulation capacity of NK cells were strongly reduced. Tregs were enriched and the CD39+ (effector/memory) Treg strongly increased during progression.

Discussion:

We successfully targeted DLI to the tumor site by RHT. Remission may be mediated by the upregulation of heat shock proteins (HSP) during hyperthermia and subsequent activation of host natural killer cells. Additionally, donor CD4 and CD8 T

cell-mediated GvT effect enhanced by DLI as well as donor NK cell response may potentially contribute to remission. The precise molecular mechanism underlying the antitumor effect observed in our patient has yet to be elucidated.