9. CLINICAL CASES 1

1032 / Oral • Can nanotechnology help immunotherapy in glioblastoma multiforme? Tumor protein loaded nanoparticles.

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INTRODUCTION Glioblastoma multiforme is the most frequent primary brain tumor that despite current treatment has a dismal prognosis. Therefore a lot of effort is put in adjuvant therapies with one possibility using dendritic cells (DCs) to harness the immune system. This DC immunotherapy consists of autologous DCs ex vivo loaded with autologous tumor lysate. But the requirement for autologous cell cultures causes this therapy to be labor intensive and expensive. We believe nanoparticles (NPs) can circumvent this problem. Preclinical studies have already shown that NPs of a specific size can efficiently be taken up by DCs and moreover induce a specific migration/maturaton of these DCs. Advantages of using NPs are decreased cost for the production of the vaccine and the possibility to create large scale products.

AIM The aim of this study is to provide preclinical evidence to replace ex vivo generated DCs by NPs to serve as a carrier for the lysate. Within the body these nanoparticle-antigen conjugates can enter DCs and elicit a specific immune response against the conjugated antigen.

METHOD Lysate from tumor cells of the GL261 mouse glioma cell line was conjugated with polyethylene NPs (NP-GL261-L). After optimization and extensive in vitro testing, we were able to conduct in vivo tests of the therapy. Therefore we used an orthotopic intracranial mouse models with prophylactic immunotherapy 14 and 7 days previous to tumor inoculation.

RESULTS At first, the NP-GL261-L therapy was tested in our standardized GL261 glioma model with prophylactic intraperitoneal injection. Compared to controls, NP treated mice showed a significant increased median survival. Because DCs reside more in the meninx and subeuros, we next tested subcutaneous injections of the NP-GL261-L conjugates. As hypothesized, this subcutaneous injection route gave an even better survival result than intraperitoneal treatment. We then compared both DC and NP-GL261-L therapy via subcutaneous injection route. The same amount of lysate was conjugated to NPs as was loaded to DCs. Both treatment strategies resulted in an increased median survival compared to untreated mice. Finally, we tested whether NP-based immunotherapy was also effective in another mouse glioma model. Therefore we used the CT2A mouse glioma cell line in the same setting as the GL261 cells. Subcutaneous treatment with NP-CT2A-L showed comparable beneficial results in the CT2A model as compared to the GL261 model, with a significant better median survival than the control injections with PBS.

CONCLUSION We conclude that NP-glioma-L therapy is an effective treatment in 2 different orthotopic mouse glioma models. The technology allows cheaper and large scale production as compared to DC immunotherapy, and can form a platform to add immunomodulatory agents.

1041 / Oral • L’impact d’un programme régulier d’érythrocytaphérèse sur les complications de la drépanocytose.

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INTRODUCTION Depuis le mois de septembre 2012, une cohorte de patients drépanocytaires du service d’hématologie pédiatrique du CHR de la Citadelle de Lègue bénéficie d’un programme d’échange transfusionnel automatisé appelé érythrocytaphérèse (EPD). Cette technique offre une multitude de bienfaits physiques et psychosociaux au patient pour autant que des ressources humaines, matérielles et financières soient disponibles.

AIM Cette étude vise à déterminer les avantages, la sécurité, les difficultés, et l’efficacité thérapeutique de l’EPD pratiquée chez des enfants et des adolescents drépanocytaires.

METHOD La population étudiée se compose de six patients drépanocytaires ayant bénéficié de l’EPD entre septembre 2012 et janvier 2015. Les critères d’inclusion sont des crises vaso-occlusives (CVO), des paludismes aigu à répétition engendrant des hospitalisations fréquentes, un syndrome thoracique aigu, la prévention primaire et secondaire d’un accident vasculaire cérébral (AVC), la surcharge en fer ne répondant pas au traitement chélateur. Pour bénéficier de cette technique, l’enfant doive peser au minimum 25 kg et posséder un abord veineux permettant le placement de deux cathéters de gros calibres.

RESULTS Six patients drépanocytaires, âgés de 9 à 18 ans ont bénéficié d’un programme d’EPD. Quatre ont été inclus pour CVO à répétition, un pour paludisme à répétition, et un dernier après la survenue d’un AVC. Parmi eux-ci, cinq patients étaient surchargés en fer malgré un traitement chélateur.

CONCLUSION Cette technique est innovante et utilisable chez les enfants. Elle permet d’améliorer l’état de santé des patients drépanocytaires. Une réduction significative de la surcharge en fer a été observée. Une efficacité thérapeutique sur les manifestations cliniques de la drépanocytose a été démontrée. Le principal facteur limitant est l’abond veineux. Pour pallier à cet écueil, deux patients ont bénéficié du placement d’une fistule artério-veineuse qui rend la technique d’EPD plus aisée et plus rapide. De plus, le patient bénéficie d’une meilleure qualité de vie grâce à l’absence de crise vaso-occlusive, à la diminution de la fatigue et à la réduction des hospitalisations.

1054 / Oral • Interventions and complications during interhospital transfer of critically ill children.

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INTRODUCTION Many critically ill children are admitted each year to hospitals that do not have a pediatric intensive care unit (PICU). Considering it useless or dangerous, doctors in these hospitals may hesitate to transfer these young patients to specialized centers.

AIM The purpose of our study is to demonstrate that these transfers are part of an optimal pediatric care system.

METHOD The charts of 1880 children transferred by our PICU transport team between 2001 and 2011 have been reviewed for this retrospective study. 13 patients died at the referring hospital. The others were admitted to our hospital or to another university hospital.

RESULTS Mean age was 23 months. Major indications for transfer were respiratory (n=481) and cardiac (n=300) diseases. The medications most frequently prescribed by the retrieval team before departure were sedatives, opioids and neuromuscular blocking agents, given to respectively 15.6, 12.2 and 14.0% of the children. 25.7% of the transferred patients required invasive respiratory support and 10.4% inotropic support. An attending staff was present on half of all transfers. 15.2% of the children improved before departure from the referring hospital and 9.5% during transport. Less than 2% arrived in a worse clinical state. At least one adverse event occurred in 13.5% of the transfers. Complications were medical in 6.3% and technical in 6.5% of the transfers; some cumulated both types. Most of these complications were reversible. However, there are any consequences of the clinical status of the children. Only 12.4% of the patients who met problems during transfer arrived in worse condition; however relationship between complication and outcome is not clear. Two factors were significantly associated with an increased risk of complications the need for a respiratory support (p<0.002) and an initial cardiac, respiratory or surgical problem justifying the transfer (p=0.0029). Age, time required for initial stabilization and total duration of transfer had no impact on the complications rate. A higher number of interventions and a longer average stabilization time were observed when an attending staff was part of the team (p<0.001). It had no influence on the complications rate despite the fact that these patients could be considered as more unstable.

CONCLUSION Interhospital transports of critically ill children can be carried out if the retrieval team is reinforced for the most complicated cases, ensures optimal stabilization of the patient before leaving, uses adequate equipment and is able to promptly react in case of unexpected events. If these conditions are fulfilled, transfer of critically ill children to a PICU can be done safely.

1078 / Oral • Cognitive functioning of childhood ALL or NHL survivors and links with biomarkers during treatment.


INTRODUCTION Contemporary treatment possibilities markedly increased survival in children NHL or ALL, the most prevalent pediatric cancers. However, chemotherapy-induced neurotoxicity - a condition in adult medicine termed ‘chemobrain’ - appears to cause long-lasting functional deficits. In a population of survivors, previously we reported increased levels of biomarkers of neurotoxicity in the CSF of children during their treatment for ALL or NHL as well as early specific information processing difficulties, though long-term cognitive function and a link with biomarkers and genetic susceptibility was never reported before.

AIM 1 To describe long-term neurocognitive functioning of childhood ALL and NHL survivors 2 To explore a potential link between biomarkers of neurotoxicity during treatment and genetic susceptibility and neurocognitive outcome.

METHOD Thirty-five childhood ALL (n = 28) and NHL (n = 7) survivors (median time since treatment 13.03 years, range between 9.42 and 15.61 years) and 35 sex and age-matched controls were included in our study, which included neurocognitive assessment, questionnaires and analysis of the 677 and 1296 polymorphism of the MTHFR-gene, encoding for the MTHFR-enzyme, which plays a key role in one-carbon metabolism. Ten patients performed equal to controls concerning baseline speed and number of errors. However, they were significantly slower on tasks assessing focused, divided and sustained attention as well as cognitive flexibility and memory, ever after correcting for socio-economic status and intelligence. Moreover, we found interactions with the task difficulty. These observations were reflected in higher scores on self-reported cognitive dysfunctions, whereas no differences on self-reported quality of life, or depressive or anxiolitic state were reported. The link with increased levels of biomarkers of neurotoxicity during treatment and genetic susceptibility is still being investigated.

CONCLUSION We confirm the early described specific cognitive difficulties and demonstrate the long-term impact of chemotherapeutics on the brain. Furthermore, we explore a potential link between the neurotoxic hit during chemotherapy, the subsequent biomarker profile, the chronic neurotoxic state and the final neurocognitive outcome. The Impact of this study is at multiple levels. Defining a panel of biomarker changes during treatment that are predictive for later neurocognitive dysfunctions will have influence on the design of future trials interventions can be investigated to protect the developing brain, new treatment protocols can be evaluated at an early stage of implementation for neurotoxicity. The study might also be important for the individual patient exhibiting MTHFR polymorphism can be stratified to be treated with adapted chemotherapy protocols, children who show during treatment a profound biomarker change that is predictive for neurocognitive dysfunctions afterwards can be helped at an early stage with appropriate learning plans.