First clinical experience with a new generation of fast DCs transfected with mRNA from hTERT, survivin and autologous tumour

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ORAL SHORT TALK
Clinical Trials

We have previously shown in preclinical models that a new generation of fast DCs, using a maturation cocktail containing IL-1β, TNFα, IFNγ, PGE2 and the TLR7/8 ligand R848, is more efficient than the standard 7 day DCs. These DCs show a high up-regulation of HLA-DR and co-stimulatory molecules like CD80, CD83, CD86 and CD40 combined with a down regulation of CD14. They have a good migratory capacity towards CCL19 and are especially characterized by IL-12p70 production when stimulated with CD40L transfected mouse fibroblasts, whilst IL-10 production is low.

Here we investigated if the new generation DCs maintain their properties when produced by GMP standards and if they are able to mount specific immune responses in patients.

Monocytes were enriched using the Elutra cell separator and cultivated either fresh or after cryopreservation. Monocytes were cultured in Teflon bags in the presence of IL-4 and GM-CSF and the maturation cocktail was added on day 2 or 3. After 24 hours DCs were harvested and electroporated with mRNA. After 2-4 hours recovery, cells were frozen with either 2.5E+6 or 5E+6 transfected DCs per vial. Productions from one lung cancer, one prostate cancer and 4 glioblastoma patients showed the same characteristics with only some slight variations in the amounts of IL-12p70 released after co-culture with CD40L transfected mouse fibroblasts.

The first patient treated with the new generation DCs transfected with hTERT and survivin mRNA suffered from stage IV lung cancer with brain metastases. Following diagnosis in June 2011 she was treated with chemotherapy and radiotherapy. Since December 2011 she has been vaccinated and has obtained a status of stable disease. DC vaccination was interrupted in 2/2013 when an attempt was made to re-open an occluded bronchus with radiotherapy. During irradiation the patient developed an inflammation of the pleura, which was treated with high dose cortisone. During cortisone therapy the patient developed 2 new brain metastases, which were treated with Dexamethasone and local radiotherapy using Cyberknife. DC vaccination was continued in 6/2013 and health conditions gradually improved bringing the patient again into a status of stable disease.

The second patient receiving DC vaccination had a hormone resistant prostate cancer in a very advanced stage and dropped out immediately after start of treatment.

Treatment of four glioblastoma patients with hTERT and survivin transfected DCs plus either with autologous tumour mRNA or hCMVpp65 mRNA DCs has started. All patients show strong local DTH responses and flu-like symptoms after vaccination at an earlier time point, but it is too early to evaluate clinical outcome.

Altogether our results show that the new generation DCs can successfully be used clinically in different kinds of cancer. Whether the strong DTH reactions and flu like symptoms observed following the DC vaccinations turn into strong specific T-cell responses is under investigation.