"The fight against Cancer pays off"

Newsletter
Defence Against Cancer Foundation
Number 1, January 2017

Friends of the ATK Foundation,

Enclosed is the latest edition of the ATK Foundation newsletter. As you may have noticed, immunotherapy has been the focus of a lot of media attention recently. This newsletter provides an overview of current and new immunotherapeutic activities. At last, in April 2016 dendritic cell vaccinations were provisionally included in the basic healthcare package. As a result, we can now embark on a study involving over 200 melanoma patients. This is vitally important and the fact that our government and the health insurance companies will now be taking part constitutes a real breakthrough! This edition includes a glimpse behind the scenes, information about newly launched studies - also on prostate cancer (Harm Westra), recently published scientific publications by Gerty Schreibelt, as well as an item on our fund-raising efforts. You will naturally also hear from our patients, because they are the reason why we apply our creative energy in this research and clinical practice, partly thanks to your support. All the contributions by everyone who supports our ATK Foundation are essential in this process.

Many thanks!

To summarise, lots of information and background stories.

I hope you enjoy reading this newsletter

Professor Carl Figdor, Department of Tumour Immunology, Radboudumc

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Dendritic cell vaccinations for uveal melanoma

Uveal melanoma is a rare form of cancer that affects only 3% of all patients with melanoma. The primary tumour in the eye is treated surgically or using a radiation technique. Ancillary (adjuvant) treatment to reduce the risk of developing metastases is not available. Such metastases usually develop in the liver, but can also occur in other organs, such as the lungs, bones, skin and lymph nodes. Metastases of uveal melanoma are virtually impossible to treat. In rare cases, local treatment such as liver surgery is an option. It is currently not clear whether the new immunotherapies for skin melanoma are also effective for uveal melanoma.

In 14 patients with metastatic uveal melanoma, we saw that it was also possible to cause an immune response using dendritic cell therapy in them. As is the case for patients with metastatic skin melanoma, this immune response was achieved in approximately 25-33% of the patients. However, the immune system is weakened in patients with metastatic disease and the tumour itself is capable of combating an immune response. Therefore, immunotherapy will probably work better for patients with few tumour cells.

In a recent study, uveal melanoma patients were vaccinated immediately after treatment for uveal melanoma (removal of the eye or radiotherapy). These patients had no metastases but they did have a high risk of metastases due to a specific genetic abnormality in the tumour cells (monosomy 3). These patients were more likely to exhibit an immune response after vaccination than uveal melanoma patients with metastases to the organs: approximately 75% of the patients. This is comparable to the results for adjuvant dendritic cell vaccinations following lymph node surgery for a large group of patients with skin melanoma. Furthermore, we saw that patients in whom we were able to provoke an immune response by means of vaccinations lived longer than patients for whom we could not provoke an immune response. The number of uveal melanoma patients is too small to draw any definitive conclusions about the effect of preventative dendritic cell vaccinations in this special subgroup with uveal melanoma.

Dr Kalijn Bol, doctor of internal medicine in training, Radboudumc

The pinnacle: Dendritic cell vaccination included in the basic health insurance package

The Department of Tumour Immunology at Radboudumc has been studying the biology and clinical use of dendritic cells for many years and is making every effort to ensure that dendritic cell vaccination becomes a standard treatment for melanoma. In the spring of 2016, the Minister of Public Health and the Environment made an important decision to provisionally include dendritic cell vaccination in the basic healthcare package. Over the next 5 years, around 20 million euros will be available to demonstrate in a large group of patients with melanoma that this cancer will return in fewer patients (as a result of vaccination).

Due to their antigen-presenting and conducting role, dendritic cells are very suitable for provoking powerful immune reactions against tumours. In the Tumour Immunology Laboratory, we create new dendritic cells using the patient's own cells. Once administered, these are activated and instructed to stimulate the patient's immune system, in order to clear up the cancer cells. These vaccinations were found to cause virtually no side effects and to be quite effective.

After years of applying dendritic cell vaccination to a limited number of patients, Radboudumc can now test this new and promising vaccination in a large group of patients. Dendritic cell vaccination will be given to patients with melanoma that has spread to the regional lymph nodes. This promising new treatment will be compared to the standard care. The aim is to ensure that the good results are not merely due to the fact that only the patients with the best chances of survival are - accidentally - selected. For the first time, health insurance companies will reimburse the costs of this treatment. After the study, the reimbursement will continue if the results show that dendritic cell vaccination has had a favourable effect. Radboudumc will perform the study together with other hospitals in the Netherlands. The first clinical evaluations are expected in 2020.

Professor Jolanda de Vries, Department of Tumour Immunology, Radboudumc Nijmegen

Experience of a patient treated in a study context with dendritic cell vaccinations for metastatic prostate cancer

Nano MRI (a new form of MRI with miniscule iron particles)
At the start of the examinations, you receive an infusion of iron particles that causes any part of your organs and bones that is affected by cancer (no matter how small) to contrast black with its surroundings. Professor Barentsz demonstrated this beautifully during his lecture at a recent meeting of contributors to the Prostate Cancer Foundation in Ede. The procedure is repeated at the end of a vaccination cycle, to check whether the areas of cancer have become smaller.

White blood cell apharesis
The white blood cell collection takes place in the Haemapheresis Department. The white blood cells are collected from the blood via two infusions connected to a special centrifuge in a process lasting 4 hours. To the disappointed lay person, the small bag of white blood cells looks like it contains murky water. This bag is then taken to the Department of Tumour Immunology's clean room. Here the dendritic cells are isolated, activated and loaded with tumour-specific proteins. This part is performed by dedicated research technicians at the Tumour Immunology Laboratory, under the supervision of Professor Jolanda de Vries and Dr Gerty Schreibelt. All in all, this is a very meticulous treatment of the material, as explained to me in advance by Harm Westdorp, my contact person there.

Vaccinations in the lymph nodes using ultrasound guidance
The next phase of the research project again takes place in the Department of Radiology. Using ultrasound guidance, the radiologist administered two vaccinations in my right lymph node. I could see clearly on the screen how deep the needle went in, but I amazingly felt nothing during any of the three injections.

Skin tests
These were performed by Harm Westdorp on various parts of my back. He warned me before starting that it would be painful. However, because I had once received Ayurvedic training in Somatheeram (Kerala), I can bring myself into a state of sleep. In the Department of Dermatology, several skin samples were removed from my lower back. I think it took about half an hour. I went to sleep immediately and suddenly woke up when a mobile phone rang. When I asked how much longer the procedure was going to take, I was told that it would only be another 10 minutes. I experienced these consciously, but looking back it was not bad at all.

Experience
My partner - Nanny de Vries, who died of pancreatic cancer on 4 July 2012 - was still able to take me to my appointment with Professor Winald Gerritsen in the VUmc, after I had been diagnosed in the OLVG in November 2011 with prostate cancer that had spread to the bones. It turned out that we were both scientists and even though we worked in totally different disciplines, we had an instant 'click'. When Winald Gerritsen was offered a position at Radboudumc, I followed him to Nijmegen. On 24 September 2015, his closest associate - Harm Westdorp - showed me a captivating video showing soldiers attacking the cancer cells in increasing numbers and eventually destroying them. All the procedures I described above are actually the preparations for this attack, which aims to achieve cutting-edge results in immunotherapy and in which radiology involving nanotechnology plays a crucial role. My role was to be the first study subject in a series of 21 other patients who would help make immunotherapy for prostate cancer a reality. I regard my participation in this ongoing study as a tiny cog in a fascinating project, a small part of it - no more, no less.

To me, the members of all the departments involved in this study are passionate about their work and will do everything they can to ensure that the various procedures fit together seamlessly. I was actually quite amused when Harm Westdorp asked me to be careful when I travelled to Rojava (Northern Syria) in October 2015 to teach a Masterclass in Kurdish history and archaeology at the Mesopotamian Academy in Qamishlo: he obviously didn't want to lose his study subject yet!

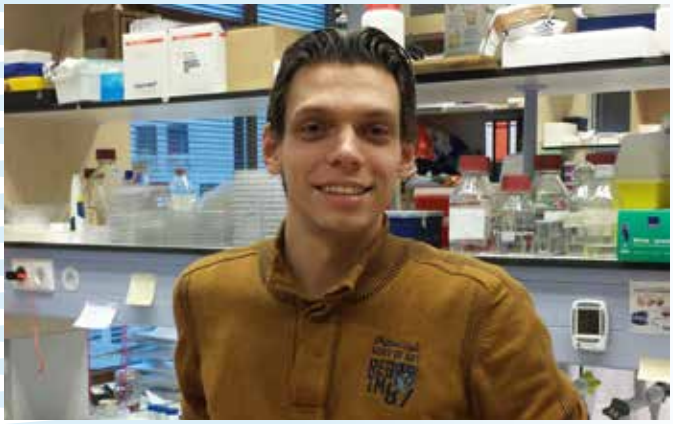
I want to take this opportunity to offer my sincere thanks to the staff of the Department of Medical Oncology. They took it in turns to collect 11 tubes of blood from me every visit and towards the end of the year they always sent me a card with all their signatures, wishing me all the best: such a kind gesture!

Travelling from Baarn to Nijmegen by train has become a day out for me. In the dining room of the lovely restaurant at Radboudumc, I often look up to where the ceiling seems to touch the heavens, a religious moment...

Dr Jan G.P. Best (patient)

Dendritic cell vaccinations for metastatic hormone-refractory prostate cancer patients

In a previous newsletter, we reported that we were setting up an experimental immunotherapy treatment for prostate cancer patients. We can now tell you that the study treatment involving dendritic cell vaccinations for metastatic hormone-refractory prostate cancer officially started at the end of 2015!



Harm Westdorp, physician investigator and medical specialist in training, Radboudumc

During this vaccination study, we will try to use a new type of dendritic cells to activate the immune system against specific proteins that occur on the prostate cancer cells of the patient. We will be testing this in three different compositions of the vaccine.

Dendritic cells are 'the explorers' of our immune system, so they are the perfect choice for use in activating the solider cells of our immune system - the T-cells - in the lymph nodes. The T-cells will then start searching elsewhere in the body for these specific pieces of protein, which they will find almost exclusively on prostate cancer cells. An immune response against the prostate cancer cells can then be activated by the T-cells, aimed at killing the cancer cells.

In this study, we firstly want to demonstrate that dendritic cell vaccinations using the new dendritic cell vaccine can actually strengthen the immune system in patients with metastatic hormone-refractory prostate cancer. We also want to investigate whether the vaccinations are safe and applicable in clinical practice. Besides the effects of the vaccine on the immune system, we obviously hope to see the vaccinations having an effect on the PSA levels and on the metastases of the cancer. PSA levels will therefore be determined every 6 weeks during this study and imaging examinations will be performed at several points using a special nano MRI scan and/or a PET-CT scan, the so-called PSMA PET-CT scan.

Finally, we will also examine the effect of our study treatment on the patient's quality of life by asking him or her to complete various questionnaires.
So far, dendritic cells have been harvested from the blood of two patients. The first patient has already received a cycle of three vaccinations and the other is due to receive the first vaccination shortly. In total, we plan to treat 21 patients with metastatic hormone-refractory prostate cancer in a study setting. We expect all 21 scheduled patients to have embarked on the study treatment by the end of 2016.

Harm Westdorp, physician investigator and medical specialist in training, Radboudumc
Winald Gerritsen, medical oncologist and professor of immunotherapy, Radboudumc

Remembering Geraldine Howard

Geraldine Howard, Co-Founder of Aromatherapy Associates, had a truly refreshing outlook on life which empowered those around her. Despite facing health setbacks throughout her life, her positive attitude never wavered.

When faced with major surgery in her early thirties to remove a non-malignant pancreatic tumour, Geraldine overcame this life changing hurdle by exuding positivity, courage and determination. She was always a generous, caring person and her mission when she co-founded Aromatherapy Associates was to share the powers of essential oils with as many people as possible.

Geraldine's resolve was tested once more in 2011 when diagnosed with a rare eye cancer, Geraldine turned to her essential oils to help ease the side effects of the innovative treatment she was undergoing and created Inner Strength, a personal blend that launched to help others through challenging times in their lives. At the heart of everything, Geraldine used her knowledge of essentials oils and didn't let one moment of uncertainty taint her outlook on life.

Teaching us that not one moment defines us, but how we continue on our path in the face of change and remaining positive, courageous and humble throughout.

Leaving behind a lasting legacy behind in the form of Aromatherapy Associates, Geraldine created a catalogue of products which continue to instil strength, peace and the ability to take comfort in one's personal space and take control of their emotional path and ability to cope with stressful times. Once quoted saying her ability to cope with stress can be accredited to the therapy training she undertook, the products she created are an essential tool in helping others find their inner strength.

The journey is finished, the adventure continues...

My 10 year journey with dendritic cell vaccination at UMC Radboud ends in September 2016. Browsing through my logbook – that I have kept since the start of the project in 2006 – I remember the 'bumps' in the road during this very special journey for me and my family.

2006 – The start of the treatment.
In 2004, I was diagnosed with malignant melanoma on the right side of my chest. In 2006, I developed metastases to the lymph nodes of my right armpit. A number of lymph nodes and my right chest muscle were removed. At the same time, in 2006 - as a Stage III melanoma patient – I embarked on the experimental dendritic cell therapy at UMC Radboud in Nijmegen. Despite developing a recurrence in the right armpit between the second and third treatment periods, I was allowed to continue receiving the treatment. Professor Punt (Medical Oncology) and Dr Bonenkamp (Surgery) acted as my guides throughout this period. From the start, this tandem team - who take it in turns to be the leader - has been my compass in the 'jungle' that is the world of melanoma and cancer. In 2008, I wrote an article for the Stichting Melanoom (Melanoma Foundation) about my initial experiences with dendritic cell vaccination and I was able to report that extra dendritic cell activity against my cancer cells had been measured in my skin and blood samples. The Stichting Afweer tegen Kanker (Immunity against Cancer Foundation) posted this story on its website.

Half yearly check-up
At the start, the dates for my half yearly check-ups in the Medical Oncology and Surgery departments had not yet been synchronised. During that period, I made the three hour round trip to Nijmegen four times a year. I was nervous every time I went for a check-up. The moment I entered the parking garage of UMC Radboud and heard the sound of the extraction system in the parking garage was the moment I realised I had entered the world of the teaching hospital. I made my way to the Red outpatients' clinic. After completing the digital check-in procedure and placing my appointment card in the red tray, I would sit in one of the comfortable chairs and enjoy a cup of coffee. Each time I was impressed by the calm and friendly approach of the nursing staff. Professor Punt would always come and collect me personally. He would ask me about anything unusual that had happened, the use of medication and he would check my liver and lymph nodes in the groin and armpits. 'I am satisfied,' was always his short and concise answer after the examination.

Then it was the trainee dermatologist's turn to screen my skin from head to toe. Fortunately, she did not detect any blemishes either. Following this short routine check, we would say goodbye and as we were standing in the doorway, Professor Punt would add: 'And pass on my regards to your wife.' 'He still remembers, I'd think to myself.' Less than two years previously, I'd been sitting at his desk crying when he had to tell my wife and I that I had suffered a recurrence, but that the situation was not hopeless and that I could continue with the treatment. It took less than 10 minutes for him to convince me. His formal, analytical approach with a personal touch is what appealed to me.

Bicycle repairman: an honorary title!
The second part of my half yearly examination consisted of a visit to Dr Bonenkamp in the Department of Surgery. He would carefully inspect my wounds and the lymph nodes in my armpits and neck. I joked with my surgical oncologist that I sometimes compared him to a 'bicycle repairman'. 'Now I am a bicycle repairman,' he laughed. 'Yes,' I said to him, 'but it's an honorary title!' I told him about the bicycle repairman who used to live in our neighbourhood. He was a true professional who 'inspected' the bikes in his greasy blue overalls. He would first shake the bike a bit, then turn the handlebars and finally step on the brake. Then he would tell you exactly what was wrong with the bike. And he'd be right too! At the end of my doctor's appointment, a blood sample would be collected to check my so-called S-100 biomarker. The S-100(B) marker is a tumour marker that measures substances produced by the body in response to cancer or produced by the cancer itself. A value above a certain threshold could be an indication of a possible melanoma metastasis in my body. After three weeks, the doctor would call me to tell me the results. This same check-up procedure was repeated every six months. I have always been diligent about attending the check-ups and I have never even changed a single appointment in those 10 years. My health is important to me and they always treat me with courtesy and professionalism in the UMC Nijmegen.

A scare
After several years, I saw Professor Punt's deputy a few times during the melanoma check-ups. This made me feel slightly uneasy. I could never get a clear answer about the situation when I asked about it. Some time later I received a letter from Professor Punt, informing me that he had moved to the AMC. I noticed that this goodbye hit me harder than anticipated. I wrote him a letter to thank him for his efforts. Dr Bonenkamp was now at the helm and I was glad to know that one familiar face remained.

One evening about a year later, I had everything packed and ready to travel to the Dutch Caribbean for 14 days for my work when Dr Bonenkamp called to tell me the result of the S100 test. The marker was too high, which meant that extra tests would be started to check my organs (X-rays and ultra-sounds). I was quite scared and asked him whether I could still travel to the Dutch Caribbean. 'Yes, of course, no problem!' he replied. 'This isn't urgent and I'll schedule the appointments,' he said. There was a surprising turn in the conversation when Dr Bonenkamp asked me if I was also travelling to Saba. 'Aha,' I thought, 'is there a point of recognition here?' We casually discussed plane landings on Saba (Saba has the world's shortest runway. To indicate that things could be worse, people often joke: 'I've survived the landing on Saba'). After this 'small talk' about the Dutch Caribbean, I felt that I'd recovered from the initial shock too.

The examinations were performed three weeks later and as soon as I entered his consulting room, Dr Bonenkamp informed me that nothing unusual had been found. However, just to be sure, he wanted to check the S100 once more. Three weeks later I returned to his consulting room. The result was good. Perhaps something had gone wrong in the laboratory and I heard him say to the trainee doctor 'and that's why you need to be careful using the S100 result'. 'And that's exactly what he does,' I told the pioneer of the S100. At that time, Dr Bonenkamp was one of only a few doctors using the S100 test. Now, several years later, the S100 has been included in the melanoma treatment guideline.

Continuity

In the meantime, I got to know my new medical oncologist: Dr Koornstra. This took a while, but I gradually warmed up to him. He suggested appointing a case manager for the combined appointments with Surgery. 'Ah, someone to act as a sounding board,' I thought. This impression was confirmed during the next appointment with Dr Koornstra, when the skin screening revealed a small area on the back of my shoulder, probably a basal cell carcinoma. He saw that this took me by surprise and reassured me that I could grow old with this. He quickly scheduled appointments with Dermatology and after a few weeks the results were favourable: no abnormalities, a benign area, probably left over from an infection. During the follow-up appointments, Dr Koornstra and I got to know each other a bit better and I noticed that he was also doing his best to establish a good relationship with me.

The home straight

In the spring of 2016, Dr Koornstra and Dr Bonenkamp both noted that my time in the dendritic cell vaccination study would end in the autumn of 2016. We can say that the experimental dendritic therapy had a favourable effect for me and helped prevent cancer cells recurring in my body. It was an exciting journey. It was a journey with few side effects. The map was clear from the start and I knew where we were heading. Looking down the home straight with the finish in sight - with all the honours going to my doctors at UMC Radboud over the past 10 years - the inevitable question that now arises is: 'Where to now? End the study, or continue with half-yearly check-ups?' After consulting my doctors, I opted for the latter. On the one hand, this gives me a sense of security, and on the other hand I am happy to keep in touch with the UMC Radboud. Because even though I know that my journey with the experimental dendritic cell vaccination for my melanoma has been successful, I also know that melanoma remains unpredictable. I face this new adventure with confidence. The journey is over, but where the new adventure will take me is unknown. But isn't that the case for many journeys in life...?

Henk Logtenberg, patient

Annual Report Stichting Afweer tegen Kanker (ATK) 2015

Strengthening the body's own immune system is a promising treatment method for patients with cancer. Vaccinations with dendritic cells can strengthen the immune systems of patients with cancer in a very specific way. The ATK Foundation continues to raise the funds required to enable more patients to be given DC vaccinations at Radboudumc. The ATK wants to support pioneering research, making it possible to treat more types of cancer with new forms of DC vaccinations. The ultimate goal is to prevent the occurrence of cancer in the future using DC vaccinations.

The funds raised so far allow the ATK Foundation to offer annual support to projects worth a total of no more than € 100,000. Projects involving the testing of new methods, techniques or initiatives are a priority for the ATK Foundation.

The projects can be submitted to the ATK Foundation on an annual basis. The submission procedure consists of two steps to make the process as efficient as possible: a preliminary notification with submission date no later than 15 December. The preliminary notification consists of the title, the project leaders, the collaborating departments and a brief description of the aim of the project (maximum of 5 lines).

The independent Scientific Advisory Board of the ATK Foundation will then select 2 or 3 applications to submit a full application, which it will then assess and prioritise. The board of the ATK Foundation decides on the allocation of the subsidy during its spring meeting.
The Foundation acquires funds through, among others:

- campaigns, grants and donations;
- endowments, bequests and legacies;
- donations.

The Foundation received a total sum of € 64,385.14 in donations in 2015. This amount is used entirely for research projects. A total of 3 board meetings took place in 2015. During the meeting in April, it was decided to award a sum of € 50,000 to the project applications listed below.

1. Prophylactic vaccination with PD-L1/L2-silenced minor histocompatibility antigen loaded DC vaccines to boost graft-versus-tumor immunity after allogeneic stem cell transplantation (Dr H. Dolstra, Dr W. Hobo and Dr M. Schaap)
2. Natural dendritic cells for immunotherapy of chemo-naive metastatic castration-resistant prostate cancer patients

(I.J.M. de Vries, H. Westdorp, J. Witjes and W. Gerritsen)

Dendritic cell vaccination for metastatic melanoma using dendritic cells from the blood

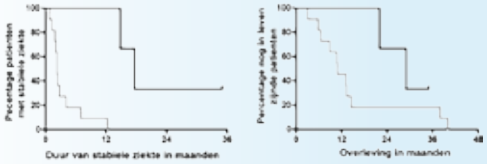
In 2010, we embarked on a study involving a new type of dendritic cell that could be isolated directly from the blood: the myeloid dendritic cell. In previous studies, we had always used dendritic cells that had been cultured from precursor cells in the blood. For a number of years, it has now been possible to isolate naturally occurring dendritic cells directly from the blood. Two types of dendritic cells occur in the blood: plasmacytoid dendritic cells (pDCs) and myeloid dendritic cells (mDCs). In this study, patients with stage IV melanoma were vaccinated using mDCs that occur naturally in their own blood.

Following blood sample collection, the dendritic cells were isolated directly from the blood using magnetic beads, which bind directly to the dendritic cells. The isolated cells were cultured overnight, to make them even more potent and loaded with protein fragments characteristic for melanoma.

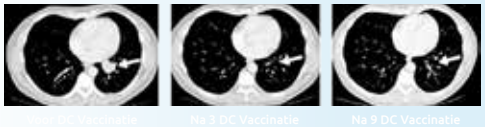
A radiologist then injected the mDCs loaded with tumour proteins directly into a lymph node, aiming to provoke a specific immune response to these melanoma protein fragments. Patients received three vaccinations, with an interval of two weeks between each vaccination. A skin test was performed after three vaccinations, to check whether there had been an immune response against the cancer cells. Patients whose disease was stable after 6 months were eligible for a second cycle of 3 vaccinations and a skin test, followed by a third cycle after another 6 months.
In total, fourteen patients with stage IV melanoma were vaccinated using mDCs during this study. We saw a clear immune response in a number of patients, both in the blood and in the skin biopsies. These patients who exhibited a specific immune response to the tumour proteins were also found to exhibit stabilisation of the disease. In two patients, the metastases decreased in size and in one patient they disappeared alto-

gether, as can be seen on the photograph. The disease is still absent in this patient after 3 years.
These results are very promising. They show that dendritic cells that occur naturally in the blood of the patients can provoke powerful immune reactions against tumour cells and that the immune cells can cause the metastases to decrease in size or even disappear completely. In a follow-up study involving patients with stage III melanoma, we are currently investigating whether vaccination with the combination of various types of naturally occurring dendritic cells - pDCs and mDCs - can result in an even stronger and more prolonged immune response.

Gerty Schreibelt, immunologist, Radboudumc



Patients with immune response (black line, 3 patients) have a longer stable disease period and longer survival than patients without an immune response (grey line, 11 patients).
Published in Clinical Cancer Research 2015.



Cross-section of the trunk at the level of the heart and lungs. On the left-hand photograph, taken before the start of DC therapy, a metastasis is visible as indicated by the arrow. Following the first cycle of three vaccinations (middle photograph), this tumour has disappeared. In the right-hand photograph, taken after three cycles of three DC vaccinations, the tumour is still absent.
Published in Clinical Cancer Research 2015.

Dendritic cell vaccination to intensify the anti-tumour effect following donor stem cell transplantation

Stem cell transplantation is an important treatment for patients with cancer of the blood, bone marrow or lymph nodes. The efficacy of the treatment is due to an immune response caused by immune cells (T-cells) from the stem cell donor. These T-cells are activated by patient-specific proteins on the tumour cells of the patient, resulting in these tumour cells being attacked and killed. This reaction is called the 'Graft-versus-Tumour' (GVT) effect. Unfortunately, there is a risk that a small number of tumour cells escape, creating a situation of residual disease. These incompletely removed tumour cells can start to grow again, causing the disease to return.

We have set up a study protocol to offer patients additional treatment with dendritic cell vaccines after donor stem cell transplantation in order to intensify the anti-tumour (GVT) immune response. These dendritic cell vaccines are cultured from white blood cells (monocytes) taken from the stem cell donor and are loaded with patient-specific proteins that occur on the tumour cells. This loading will be done using a method called 'RNA electroporation'. We created RNA raw materials for this purpose in a clean room and these materials code for patient-specific proteins that are found on the tumour cells of the patient.

Furthermore, we have developed a unique method to make the dendritic cell vaccines even more powerful, by removing the immune-inhibiting proteins for the so-called PD-1 receptor on the cell surface. Following the stem cell transplantation, the patients are treated with the DC vaccination three times at intervals of two weeks. Following the three vaccinations, we will measure how many specific T-cells targeted against the tumour cells have been created in the blood and bone marrow. The aim of this study is to achieve optimum activation of donor T-cells targeting proteins on the tumour cells of the patient, in order to prevent the disease from returning.
Three patients have already been vaccinated with only RNA-loaded DC vaccines. No severe side effects occurred after the vaccinations and 2 of the 3 patients exhibited an elevation in their specific T-cells in blood and bone marrow. Now that this has been proven to be safe and the raw materials for switching off the immune-inhibiting proteins have been produced, we can vaccinate the following set of patients with this improved DC vaccine.

Dr Harry Dolstra, immunologist, Radboudumc

DC vaccinations following stem cell transplantation for the treatment of aggressive lymphoma

At the start of September 2012, I strained a small muscle in my side playing golf on the computer.
On a family outing a few weeks later, I took quite a hit in the bumper cars, aggravating the pain in my side. As this was causing me considerable trouble at work and in sports, I decided to visit my GP. The GP listened to my story and told me to take things easy and take a few paracetamol for the pain. Just to be on the safe side, he referred me to the hospital for an ultrasound.

Whilst the ultrasound was being performed, a doctor was called in and I was told to contact my GP, because they wanted to run more tests. At that moment, I had no idea that my whole world was about to be turned upside down...

Within the hour, my GP called me, but the conversation was more along the lines of: 'Are you in any pain? Are you alone? Can you come here or do we need to come to you?' On my way there, I did start to wonder what was wrong. When I saw the GP, I was informed that I had lymphoma. It was so surreal that I initially thought he was joking. The penny only dropped later on, when I was in the car on the way to my parents. I had cancer. When you think of cancer, you think of death. My aunt had died as a result of this terrible disease less than a year before. With tears in my eyes, I decided to drive home first to gather my thoughts. How do you tell your parents and those around you about something like this?

From that moment, you find yourself on the proverbial rollercoaster. I had several appointments and various tests. Firstly, it is important for the doctors to find out what type of lymphoma it is, so that they can decide on the best treatment. In early October, I discovered that I have a Follicular Lymphoma: a Non-Hodgkin's Lymphoma. This is a disease that is more common in older people. The main objective was to get the lymphoma in remission (a state of rest), which meant that I would never be cured of this disease.

It was agreed that I would first start on a milder form of chemotherapy and I embarked on this treatment in good spirits. Unfortunately, things did not go as planned. I developed an allergic reaction to Rituximab, one of the pivotal drugs in the treatment schedule. As a result, the infusion took longer to administer. Instead of taking 2 hours, it took 9 to 10 hours. When I heard after 3 cycles that the treatment was not working, we switched to a different 'mild' treatment. Again I received this treatment 3 times.

This was around Christmas time and I was ready for some good news, but unfortunately there was none. The effect was minimal and when a biopsy revealed that the cancer in my lower abdomen had become more aggressive, things became very tense and I began to wonder whether I would make it. This was a very difficult period for me and the people around me.

Then it was decided to switch to the 'heavy' treatment and there was the first mention of a stem cell transplant. As the disease in my lower abdomen had become more aggressive, I would - if the treatment was effective - have to undergo stem cell transplantation, or else there was a very high risk of the disease returning. At that moment it also became very clear that this 'heavy' treatment really had to work. On the other hand, if everything went well, I would be cured of this disease. This was quite different to the original prognosis.

Everything went really quickly again after this: the doctors searched for a donor in my family. My younger brother was tested, but unfortunately was not a match. In the meantime, doctors were also looking for an anonymous, non-related donor. Hearing on 'Good Friday' that the treatment was working really made my day. I had various other tests, a sort of baseline measurement and an information day about the transplant.

In order to buy a little more time, I had one extra treatment. During this period, I learned that they had found a good match. When I went for a check-up on the Monday, I was told that I would start the process of stem cell transplantation a week later. This was another intense period that I was dreading. Looking back, the first week was not too bad, as I had already undergone various chemotherapy treatments. Unlike many patients, they did not make me feel very sick. Thank goodness, things were going my way for once. The big moment arrived on 18 June 2013 and I received the donor stem cells for the first time. Four days later, on 22 June, I celebrated my birthday and this also happened to be the last day on which I felt well. The following days were very bad and tiring, and I now understood why there was a stool in the shower.

I don't know whether it was due to the fact that I had played lots of football all my life, but my body recovered very well. So well in fact, that I finished the treatment a day or two early. A period of rest and recovery at home followed and fortunately my mother was able to care for me every day. The check-ups took place every 3 weeks and at one of these check-ups I

was told that I could take part in a study involving dendritic cells. These cells were supposed to get rid of any remaining cancer cells. It did not really feel like a study, but more like an addition to my treatment. The only thing I dreaded slightly were the bone marrow biopsies. But after everything I had been through, this was just one more thing to add to the list. Following the last biopsy, it was clear that the cells were doing their job and were present in the bone marrow.

Now, almost 3 years later, I have completed the physio. I have had all my childhood vaccinations again and I am back to working full time. I play football again and enjoying life.
I realise how lucky I have been and that no one knows what the future holds.
This is why it is so important to continue performing research.

Dimitri Gerrits, patient

Innovation in the preparation of dendritic cells: the CliniMACS Prodigy

Continuous improvement is a must! The Department of Tumour Immunology at Radboudumc is heavily involved in this. For example, the company Miltenyi Biotec GmbH has invented and designed the CliniMACS Prodigy. The CliniMACS Prodigy - a machine in which cell products can be processed in a fully automated process in a closed system - can only truly become an innovation if it has been used successfully in clinical practice.

Use in clinical practice

It sounds very simple. You buy the CliniMACS Prodigy, have the machine installed, ask for a brief explanation about how the machine works and then start using it. However, it is a lot more complicated, because it is a (new) medical device that has not been used before in experimental cell therapy.

In practice, we need to be able to answer the following two questions in detail before we can use white blood cell products from cancer patients to prepare dendritic cell vaccines that will eventually also be administered to these patients.

Can the CliniMACS Prodigy really do what the manufacturer says, also for our application?
Can we, as users, repeatedly make dendritic cell products using the CliniMACS Prodigy, which meet the quality requirements, as stipulated in the study file that has been approved by the CCMO (the Central Committee for Research Involving Human Subjects)?

By joining forces, we have been able to answer both questions in detail after performing three test sessions. During these tests, we used white blood cell products from healthy volunteers to demonstrate that dendritic cell vaccines could be prepared repeatedly to meet all quality requirements using the CliniMACS Prodigy. The benefits of using the CliniMACS Prodigy are that dendritic cell vaccines can now be fully prepared within a maximum of 4 days, that the majority of the preparation process takes place in a closed system and in a fully automated manner and that the process has become less labour-intensive.

CliniMACS Prodigy

You will no doubt be wondering: 'What exactly is the CliniMACS Prodigy?' Let me explain. A sterile, disposable set with a number of tubes is connected to the CliniMACS Prodigy via a series of valves, sensors and a pump. Next, the bag containing the white blood cell product from the patient is connected to the disposable set and the blood cell product is pumped into the set (see photograph). The cells are then collected in a centrifuge chamber and the volume is reduced. Unique magnetic beads are added to the blood cells, which bind directly to the dendritic cells. All magnetic beads that are not bound to cells are washed away and the cell product is then transported over a column hanging in a strong magnetic field. The cells are separated over this column; all dendritic cells with one or more magnetic beads remain 'attached' to the column and all other cells move through the column and are then collected in an empty bag. Once the magnetic field is switched off, the dendritic cells with a magnetic bead 'detach' from the column, move through the column and are collected in another empty bag. These dendritic cells are then cultured - in the CliniMACS Prodigy culture chamber, or in culture plates in an incubator - so that they are 'trained' to recognise tumour cells. After the dendritic cell vaccine has been administered to the patient, these trained dendritic cells will activate 'killer T-cells' in the lymph node which will then attack and destroy the tumour.

Successful?

Has the Department of Tumour Immunology now successfully implemented the CliniMACS Prodigy in practice? The answer to this question is a convincing 'yes'. On 6 November 2015, the first two patients - one with melanoma and one with prostate cancer - were vaccinated with dendritic cells prepared using the CliniMACS Prodigy. Currently, 14 patients with melanoma and 4 patients with prostate cancer have been treated with dendritic cells prepared using the CliniMACS Prodigy. As far as we are concerned, many more patients will follow and we hope that our dendritic cell therapy will be able to treat many more cancer patients in the future.

Jeanette Pots, senior research technician in the Department of Tumour Immunology, Radboudumc

What can you do to support the Defence against Cancer Foundation?

You too can contribute to the fight against cancer simply by making a donation. No matter how big or small, every gift is always welcome. Perhaps you have an idea about how to raise money, like holding a sponsored walk. Many others have led the way and maybe you can inspire even more people to help in the fight against cancer. If you have suggestions or questions, please contact: info@afweertegenkanker.nl or make your donation directly on the website: www.afweertegenkanker.nl/doneren

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