Dendritic Cell Therapy

Comprehensive Guide

What are DENDRITIC CELLS?

- Dendritic Cells (DCs) are known as antigen presenting cells. They are special key regulators of the Immune system capable of activating the T-Cells and stimulating the growth and differentiation of B-Cells. Dendritic cells identify specific protein markers known as peptides on the surface of foreign or invading cells. DCs then present these peptide markers to other cells in the immune system so that they can seek out cells that carry this specific marker and destroy them.

What is DENDRITIC CELL THERAPY?

- Dendritic Cell Therapy harnesses the action of Dendritic Cells by identifying specific antigens on the cancer cells circulating in the blood of an individual, allowing the immune system to seek out the cancer cells to destroy them. It also stimulates memory cells providing long lasting immunity.
- Dendritic Cell Therapy is not a genetic therapy.
- Dendritic Cell Therapy does not involve the use of genotoxic (chemo) drugs.

How is the DENDRITIC CELL THERAPY made?

- Individualized dendritic therapies are created by isolating the Dendritic Cells and Circulating Tumor Cells (CTCs) from a fresh blood sample of a cancer patient. The CTCs are analysed to identify the most frequently expressed protein (epitope) on the surface of these cells. This cancer protein is then imprinted on to the dendritic cells. The dendritic cell population is then augmented into millions, and the final preparation is created for administration to the patient.

What is the goal of DENDRITIC CELL THERAPY?

- The goal of the Dendritic Cell Therapy is to prime dendritic cells to teach T cells and B cells to recognize the cancer epitopes. Eventually, the CD28 T cells form memory to teach new dendritic cells to execute the same process as the initial. If the DENDRITIC CELL THERAPY is effective, it will provide the patient with long-term immunity against the cancer cells.

- Immune Frame testing is done prior to Dendritic Cell Therapy administration to establish the baseline immune system status and repeated as follow-up testing to monitor the immune system's response. Dendritic Cell Therapy "boosters" can be made in the future for the patient if the dendritic cells or the CD28 T cells lose potency or memory.

What kind of cancers can be treated with DENDRITIC CELL THERAPY?

- Solid tumors
- Theoretically, all cancers can be treated if circulating tumor cells can be found in the blood

Note: There are currently active trials using the Dendritic Cell Therapy in melanoma and kidney cancer.

What kind of cancers will not respond to DENDRITIC CELL THERAPY?

- Hematologic malignancies
- Testicular Cancer
- Compartmentalized cancers
- CNS cancers – Dendritic cells do not usually pass through the blood brain barrier to reach the target. Therefore, CNS cancers have to be biopsied in order to create the therapy and consequently are less likely to work as well as it does with other types of cancer.

At what cancer stage should a patient consider DENDRITIC CELL THERAPY?

- Any stage can be considered if the cancer is stable and the patient is not on any concurrent chemotherapy, radiation or immune suppressive therapies.
- Also appropriate for the patient that is currently in remission and seeking to reduce the likelihood of a cancer reoccurrence.

Are there any contraindications to DENDRITIC CELL THERAPY?

- Recent radiation or chemotherapy - the patient will need to wait a minimum of three (3) weeks.
  - The time frame is only an estimate and may be longer depending on the status of the patient, and their immune system's ability to restore itself. Careful evaluation needs to be done by the healthcare provider before recommending this therapy to insure optimal response.
- Recent blood transfusions – the patient will need to wait 120 days
- Active Autoimmune Disease
- Cachexia
- Pregnancy or breast feeding
- Active infections/inflammation (CRP>3.0) (Sed Rate >29 mm)
- High Tregs or TNF-a on the pre-Immune Frame. (Over 5%)

Is DENDRITIC CELL THERAPY safe?

- Multiple studies, including human trials and clinical experience have established the DENDRITIC CELL THERAPY as generally safe.

What happens if the patient's immune system doesn't respond?

- If there is not a successful response by the patient's immune system by the end of the third dose, you can either start a new DC therapy cycle with a different antigen OR change the therapeutic strategy altogether.

What is the administration schedule of DENDRITIC CELL THERAPY?

- One dose every 21 days for three total doses and two follow up tests:
    - Dose 1 – Day 0, Dose 2 - Day 21, Dose 3 - Day 42
    - Follow up Immune Frame and Oncotrace – Day 63

Note: It is critical that doses be administered on the recommended intervals to ensure optimum response. Obtaining a confirmation of commitment to the schedule by the patient is recommended prior to ordering the therapy.

Note: if the administration schedule was altered at all, then the follow up tests are 21 days after Dose 3

Important: These are live cells and need to be kept cold. Put into the refrigerator upon receipt. Do not freeze. The dendritic cells must be administered by Day 7 at latest (Shipment from lab is on a Friday (Day 1) administration must occur by Thursday of the following week (Day 7). After Day 7 the cells are no longer viable and cannot be administered.

What IS included in the DENDRITIC CELL THERAPY package and what is the cost?

- Package Price: 7900 Euro
- Package Includes:
    - All three (3) doses of the Dendritic Cell Therapy
    - 1 Follow up Immune Frame after the third dose (Day 63)
    - 1 Follow up Oncotrace after the third dose (Day 63)

- Package DOES NOT include:
    - Initial (baseline) Immune Frame (800 Euro)
    - Initial (baseline) Oncotrace (650 Euro)

What are the mandatory pre-requisite tests required to establish baseline for DENDRITIC CELL THERAPY?

- Initial (Pre) Immune Frame
- Draw: 15-25 ml of blood
- Cost: 800 Euro

- Initial Oncotrace – (Baseline CTC)
- Draw 15ml of blood
- Cost: 650 Euro

(**Reminder**: the baseline tests are not included in the cost of the actual therapy)

What are the mandatory follow up tests for DENDRITIC CELL THERAPY?

- Mandatory Follow-Up Testing: **Day 63**
- Immune Frame (included in therapy package cost)
- Oncotrace (included in therapy package cost)

Note: It is highly recommended to run a follow-up Immune Frame test every 6 months for at least 2 years to monitor CD80, CD86 and CD28 levels to determine if a booster becomes necessary. These tests are optional and not included in the original therapy package.

How much blood is required for DENDRITIC CELL THERAPY?

- Initial Immune Frame (Baseline test) (Draw 15-25 mL of blood) 1 vial
- Initial Oncotrace (Baseline test) (Draw 15ml) 1 vial
- Dose 1, 2, and 3 of DENDRITIC CELL THERAPY (Draw 70-80 mL of blood) 3 vials
  Follow up Immune Frame (Draw 15-25ml of blood) 1 vial

NOTE: if ordering the Oncotrace, Immune Frame and the three doses of the therapy at the same time then **80ml** of blood (3 vials) will be sufficient

What pre-medications are required for DENDRITIC CELL THERAPY?

- Mandatory: 4 mg dexamethasone I.V. in a 20-50 ml rapid drip saline solution or slow bolus push.
- Optional: IV H2 inhibitors: Cimetidine, Nizatidine, or Famotidine-give at least 30 min before IV.
- Optional: Paracetamol (Acetaminophen), PO 500mg, three time per day for up to three days starting an hour before the application, in order to counteract headache that could develop.

What needs to be avoided prior to the pre-Immune Frame and the DENDRITIC CELL THERAPY?

The purpose of these guidelines is to ensure the highest level of effectiveness of each therapy by removing treatments that interfere with and/or diminish the effectiveness of that therapy. Adherence to these guidelines will improve therapy effectiveness and patient outcomes.

REASON: The breakdown of the CTC caused by these substances creates debris that interferes with the therapy's ability to find its target. Allowing time for the body to clear the debris will increase the effectiveness of the therapy.

- **Pre-Therapy Administration:** The patient must be off ALL cytotoxic and free radical producing therapies. If drawing for cellular therapies, the patient must be off ALL immune suppressing therapies as well.
  - **Natural Substances** (IV): cytotoxic substances like Vitamin C or Ozone at least **14 days.**
  - **Natural Substances** (oral supplements): Class 1 cytotoxic substances (per patient's Onconomics Plus results) at least **14 days.**
  - **Chemotherapy** (non-platinum derivative): at least **14 days.**
  - **Chemotherapy** (platinum derivative): at least **21 days.**
  - **MOAB or SMW drugs** for at least **14 days.**
  - **Blood Transfusions:** at least **120 days.**
  - **Radiation**: at least **14 days.**
  - **Contrast:** at least **14 days.**
  - **Surgery** (simple/routine): at least **7-10 days.**
  - **Surgery** (brain or extensive): minimum of **30 days** based on time of recovery. Could be longer if slow recovery or if the person had some type of adverse reaction. Must be evaluated on a case-by-case basis.
  - **Fever:** at least **14 days.**

- **Hyperthermia** (local/concentrated/microwave ablation): at least **30 days** due to increase in cellular debris released into blood stream.
- **Hyperthermia** (generalized/systemic): no waiting.
- **Cryoablation:** no waiting.
- **Immune Suppression Medication** (All pre-Cellular Therapies – VAXO-Q-RE, Vaccine Prep, Dendritic Cells, DendroCov): at least **14 days.**
- **Radioactive Seeds:** Patients are not eligible for therapies due to the prolonged and undetermined time of the radiation exposure.
- **Gamma Delta T Cell Therapy (GDTC):** Patients are not eligible for therapies due to the potential interaction with RGCC therapies.

What needs to be avoided after DENDRITIC CELL THERAPY?

- The patient must stay off **ALL cytotoxic, or free radical producing, and immune suppressing therapies 21 days** after the administration of the therapy.

- Advise patient to avoid contracting Parvo 19 (parvovirus B19). This will most likely completely destroy the cellular immunity that the DENDRITIC CELL THERAPY has created, and they will have to start over, after they show that they are now immune to Parvo 19.

The above is not an exhaustive list of problematic substances, so how can you decide what might interfere with the development of memory cells?

In deciding what might or might not interfere with the development of the memory cells, ask yourself if the product has a direct or indirect effect on the CTC (in either being directly cytotoxic or in the generation of free radicals). Those are the problem substances since they create inflammation and debris in the blood sample (the scientists call it noise). Example: Artemisinin breaks down DNA so it' works directly as a cytotoxin so it must be avoided. So does substances like Ivermectin, Ozone, Colloidal Silver, and Curcumin.

However, substances that work indirectly through the metabolism of cells (starving cancer) like Salicinium or Metformin only need to be avoided for 7 days after the administration of the therapy.

Additionally, substances like Flavonoids (ALL - including Quercetin and Resveratrol) and products like modified citrus pectin also work indirectly so they also only need to be avoided for the 7 days after administration of the therapy.

Are there any possible adverse reactions with DENDRITIC CELL THERAPY?

- Flu-like symptoms
- Fatigue
- Fever
- Injection site reaction (skin rash)
- *Uticaria (hives)
- Tumor Lysis Syndrome (TLS) with large volume of tumors

*__Note__: There has never been any reported severe life-threatening anaphylactic reaction from this procedure. However, there is no guarantee that this will not happen, however rare it may be.

What are the expected results after DENDRITIC CELL THERAPY?

The end result of Dendritic Cell therapy is the decrease of CTCs and the follow up Immune Frame is showing the activation of immune system.

1)**Baseline**: Patient is not eligible for Dendritic Cell therapy if the pre Immune Frame shows:

- High Tregs (CD25 + CTLA4) (over 5%)
- High TNF-a (over 5%)

2)**Monitoring Progress**: Follow up Immune Frame for Dendritic Cells is at **Day 63**.

- Any rise of markers except for CD25, CTLA4 and TNF-a is an indication of activation

3)**Final Outcome**: **Day 63** – Immune Frame expected results:

- T&B cells should be steadily present
- CD 80/CD 86 should be over 22%
- CD 28 – B & T line should be above 0 (even barely ok)

4)**Booster is necessary**:

- If the Immune Frame at Day 63 does not show the expected results as outlined above under 3) Final Outcome.

What is the Booster policy for the DENDRITIC CELL THERAPY?

- Request must be made in writing within 120 Days from Dose 1 of the original DC therapy
- Booster will be for the same epitope target of the original therapy
- Patient must not have undergone other cytotoxic therapies (radiation or chemotherapy)
- Patient must not have undergone other conventional immune therapies

When is a new DENDRITIC CELL THERAPY order required?

- It has been over 6 months from Dose 1 of the original therapy administration
- Memory cells have started dropping (to know this information patient will require an optional follow up Immune Frame between Day 63 and Day 120). **Important**: Optional Immune frames are not included in the package price of the therapy.
- Patient has undergone conventional cytotoxic or immune therapy since receiving the original DC therapy (this will automatically require a retargeting and even if within the booster time line it will not be considered a booster).

If based on the above you believe your patient requires a booster, please follow the below steps:

1) Submit booster request to **support@rgcc-international-northamerica.com**
2) Include in your email your rationale for the booster request. Ex. Day 63 follow up the patients CD 80/86 cells did not meet the desired percentage number.
3) Include the exact dates of the therapy administration.
4) Include what therapies (conventional and alternative) the patient received post blood draw for the therapy.
5) Include what therapies (conventional and alternative) the patient received post therapy administration (if any).
6) Provide the required completed follow-up forms.

How to Administer DENDRITIC CELL THERAPY

Important: It is critical that doses be administered on the recommended intervals to ensure optimum response. There is a synchronization effect needed and it is essential the doses be added at the designated time, or the therapy will not work as intended.

First steps:

- Take the patient's Dendritic Cell therapy vial out of the refrigerator and allow it to come up to ambient room temperature while the pre medications are being given. Even warming to low normal body temperature (90-95 degrees) by holding in your hands can be very helpful as well.
- Check the vial number and match to patient's name.
- Inspect the vial. The cells are suspended in solution and are ready for administration. The solution should be colorless without any sign of precipitation. **In case of any color changes or any precipitation DO NOT ADMINISTER. Immediately notify RGCC by email at **info@rgcc-international-northamerica.com** and call 1-800-813-1372.

PRE-MEDS: Administer pre-medications prior to each dose of the DENDRITIC CELL THERAPY.

- Start with about a 250-500ml bag of saline
- Start the IV line with Catheter to the patient
- Administer the IV form of any H2 inhibitors: Cimetidine, Nizatidine, or Famotidine-give at least 45-60 minutes before the IV. If giving orally, it needs to be given 6 hours before the IV.
- Ready 4 mg dexamethasone I.V. in a 20-50 ml rapid drip saline solution or very slow bolus push
- Paracetamol (Acetaminophen), PO 500mg starting an hour before administration and up to three times per day for up to three days after administration to help counteract the headache that could develop.

Note: The use of Dexamethasone is to help prevent the likely severe damage to the surrounding tissue if the patient experienced an extravasation during the administration of the therapy.

Day 1 – 1st Dose

- Before the pre-medications are finished prepare 250-500 ml IV saline
- Remove the security tape carefully, remove cap, wipe the stopper with a sterile alcohol swab
- Leave the bottle in an upright position to remove the sample, REASON: (the inside rims on rubber seal can sometimes cause cells to stick)
- Use a 10 ml syringe with a 21-gauge 2-inch needle and very slowly remove the 5-7 ml of cells
- Slowly push the cells into the 250-500 ml saline bag, (remember to be slow and gentle). Pull back 1 to 2 times partially filling the 10 ml syringe with saline to remove all cells from the syringe
- Gently swirl/tilt the prepared IV solution a few times to mix well
- Now you're ready to infuse the Dendritic Cell drip into the patient. Drip rate should last approximately 45 minutes to 1.5 hours
- This drip should not cause any pain or discomfort to the patient. In some cases, during the IV or shortly thereafter, the patient may begin to experience a slight fever (99-100), slight headache, or chills. This is generally a good thing but monitor the patient while in your office and instruct them to call you if the fever rises over 102 degrees over the next several days

Day 21 – 2nd dose – Administer exactly the same as dose 1.

Day 28 – Optional Follow up Immune Frame – Optional - Not included in package

Day 42 – 3rd dose – Administer exactly the same as dose 1 and 2.

Day 63 – Mandatory Follow up Immune Frame and Oncotrace – Mandatory - Included in package

What are the goals on Immune Frame post DENDRITIC CELL THERAPY?

The goal is to develop a long-term immune response:

- >30 on both CD80 & CD86 memory cells
- >1.0 on CD28 memory cells

This is done by increasing cell-mediated immunity and humoral immunity:

- Increasing INF-γ (interferon gamma)
- Increasing IL-2 (Interleukin 2)
- Increasing IL-4 (Interleukin 4)
- Increasing IL-6

This is done by decreasing the inflammation markers (the lower the negative the better):

- Lowering high TNF-a (Tumor Necrosis Factor alpha)
- Lowering high Tregs (T regulatory cells)
- Lowering CD25 and CTLA4

Is there anything that can be done to help obtain optimal results on the follow up Immune Frame?

Yes, there are various substances that can be helpful.

- High-TNF - usually responds to curcumin—resveratrol—astragalus
- High-Tregs - usually respond to vitamin A – vitamin D3 (emulsion or micellized form)
- High-IL-6 this can usually be lowered by a homeopathic IL-10 (From GUNA), astragalus. D3, Zinc, Magnesium and Resveratrol has also been found to be helpful.
- Generally, PAW-PAW, ASCORBIC ACID, & OZONE seem to work universally.

When the above go down, the other markers (IL-4, IL-2, CD28, CD80, CD86) will be getting higher and that is the trend you want.

You want the following to be as **HIGH** as possible**:**

- INF-γ (interferon gamma) - does well with homeopathic Citomix (From GUNA)
- IL-2 and IL-4 - these will usually respond just by down regulating TNF, Tregs, and IL-6.

Q: When do you start the natural products for DENDRITIC CELL THERAPY?

- Start the natural products while waiting on the Dendritic Cell therapy to come in (usually 2-3 weeks before the infusion) and continue until the follow up Immune-Frame

Note: The only exception to the above are substances that are directly cytotoxic like Curcumin and Ozone. These should be avoided for 21 days after the Dendritic cell therapy has been administered.

Advanced FAQ from Practitioners

Q: Why did DENDRITIC CELL THERAPY change from two doses to three doses?

A: From Dr. Papasotiriou, the analysis of data after long term application shows the following:

If we rely on the Immune-Frame after each step, especially between the 1st and 2nd dose, we may lose the window of actual boosting the immune response simply because the peak is taking place on day 21 and 28. If we delay further, we may permanently lose this time opportunity.

The risk of delay is the same between doses 2 and 3 but still measurable, thus the reason you might choose to run an optional Immune Frame. Therefore, it is best to have a straight algorithm of application and tests during the process of Dendritic Cells application.

Q: Can scans look worse after DENDRITIC CELL THERAPY?

A: Yes. The Dendritic Cell Therapy is a personalized treatment and therefore the magnitude of the response varies significantly from person to person. The result of the Dendritic Cells is the generation of antibodies and specialized cells that will attack the tumor. Due to the fact that this is an immunotherapy, it is not uncommon to witness an increase in tumor mass due to the inflammation that the immune system causes while attacking the cancer cells or even a rise in some cancer markers in serum due to the fact that cancer cells are being killed and cancer proteins are released to the blood. This is known as pseudo-progression and is common in immunotherapies.

In order to see if the Dendritic Cells are activating the immune system to attack the cancer, and for how long, it is recommended to check specific immune markers. In RGCC we use the Immune Frame. It is required to have an Immune Frame before undergoing the Dendritic Cell Therapy in order to see the baseline levels, and then you can follow the response again using this test to evaluate immune activation.

Q: Can DENDRITIC CELL THERAPY be done to a person with a large tumor?

A: The goal is to activate the immune system against the patient's cancer cells. The Dendritic Cell therapy should only be administered after careful evaluation of each patients current health status. Patients with tumors in highly vascularized areas such as the lungs or liver, as well as those with a single large tumor or multiple tumors (measuring over 5 cm singularly or in total) are at high risk for an inflammatory effusion known as Tumor Lysis Syndrome which can cause severe symptoms.

Q: What antigen/protein is targeted in MBC with DENDRITIC CELL THERAPY?

A: The targets will vary (RGCC does not provide that information) with each MBC case. This is one major reason you cannot use the therapy from patient A on patient B with MBC or vice versa.

Q: When the cancer mutates to hide from this target, is another one substituted or does DENDRITIC CELL THERAPY become an obsolete option?

A: The CD80, CD86 and CD28 memory cell count will slowly go down over the months/years as the cancer mutates away from the original target. This is the reason for the constant follow-up Immune Frames over months and years. At this point the lab will need a new blood sample to create a new Dendritic Cell Therapy for these new mutated cancer cells, this is called a "Retargeting" which creates the antibodies against the new epitope of the new cancer cells/tumor. This is why the therapy can be used to help patients with two or more primary cancers at the same time.

Q: Is there a timing consideration to when SOT is being administered also?

A: It's best to wait for the results of the follow up Immune Frame before adding the SOT. The reason is that the SOT may slow down the therapy from forming the numbers you are aiming to achieve on the follow up Immune Frame. From this point on you can repeat the SOT every 4-8 months (as desired) to also work against the cancer simultaneously regardless of the immune system's level of function.

Q: Can DENDRITIC CELLS be used with Brain or Spinal cancers?

A: Not easily and it's not recommended. The reasons are that when administering primed DENDRITIC CELL THERAPY into the CSF (which means that we inject cells in a level of 10^6 cells and above) you will automatically be altering the consistency of the CSF (since none or up to 1 cell per cc should be present). Hence, the fluid itself may cause severe problems for the patient.