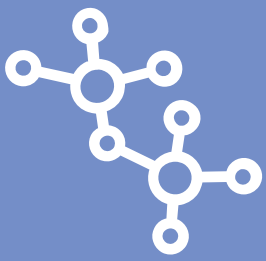
Individualized cancer therapy with specific activation of the immune system



Patient information on the
personalized immuno-oncological therapy

IOZK FOUNDATION
IMMUNO-ONCOLOGICAL RESEARCH

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Welcome to the immuno-oncological centre in Cologne

We are glad that you are interested in the immunologic treatment offer of our interdisciplinary group of experts. Since 1985, our doctors and scientists have been researching the role of the immune system in confronting cancer and chronic infectious diseases.

In recent decades, the area of tumour immunology has been the focus of intense international research, as this innovative treatment method progressively gains importance.

Our team achieved to effectively produce the first vaccine gained from patient's own cells and combined with an oncolytic virus - in accordance with the German Medicines Act for advanced therapies. Our institution has the first legal permission in Europe to produce this vaccine. This substance called IO-VAC® is made from the patient's own dendritic cells, which are loaded with the specific antigens of the patient's tumour. Unique is the combination with an oncolytic virus that is not harmfull to humans but gives an additional activation boost to the immune system. The vaccine leads the immune system to recognize the specific antigens of the patient's own tumour and attack it.

The complete cure of a tumour in an advanced stage is still rarely possible, even for this special form of therapy. However, it offers a chance to slow down the progression, since in our multimodal immunotherapy the IOZK can be combined with different types of therapy.

Our main goal is to have an influence on controlling the progress of the disease and to increase the duration and quality of the patient's life.

Immunological tolerance towards tumour cells

The immune system is the guardian of our health. Its main function consists in distinguishing between “own” and “alien”, “harmless” and “dangerous”, so as to ensure the integrity of body tissue, a state known as tissue homeostasis. Unknown substances, disease carriers and damaged cells can be eliminated this way.

In the tissues of the body, cells are constantly mutating, a process generally recognized by the immune system.

> **If cells degenerate or develop malignant growth, they will normally be detected and eliminated by the immune system. Only a misguided immunological tolerance towards malignant mutated cells can allow a tumour to develop.**

In this case, it is likely that a first immunological contact with the tumour already took place, but was not successful. However, the immune system contains memory T cells, which can be reactivated to fight the tumour once again. We use this principle as part of our innovating therapy concept.

This shows that the control mechanisms of the immune system can fail so that they no longer effectively fulfil their defensive functions. Once tumour cells have survived for some time in the body and developed into a tumour, they influence the immune system. Through various forms of biological “camouflage” they stop the attack of immune cells and manage to become “invisible” to them. The defence cells get used to the tumour and tolerate it as harmless, even if it keeps damaging the organism.

This immunological phenomenon is called development of tolerance. It can be breached through a specific immunotherapy. However, if the immune system is to take initiative of its own, it needs appropriate information on the tumour cells in order to overcome their tolerance. To this end, we can use the knowledge of the biological fundaments of immunology.

Active and passive treatment procedures

Most usual treatments of cancer so far have focused on removing or destroying the cancer cells through operations, radiation, chemo, hormone or passive antibody therapy as well as targeted therapies. The downside of these methods is that they don't differentiate between diseased and healthy cells, since they are non-specific. This means that the common therapy will always damage healthy tissue, producing according side effects. The fundamental problem with conventional treatment procedures is that the patients remain passive and things are simply “done to them”.

Immunological cancer treatment has led to a paradigm shift: our polyvalent immunotherapy with IO-VAC® aims to put the immune system into good conditions to activate itself and take up the fight against the disease. This does not require destroying up to the last cancer cell.

> **Instead, nowadays it is considered that equilibrium between the tumour and the immune system is more important – resulting in an extension of the overall survival time and an improved quality of life.**

This situation is best described as a progression-free, mestastasis-free or stable disease. The first significant increase in overall survival time was shown to have a correlation with autologous immunotherapies.

Fighting cancer with a specifically trained immune system

For the immune system to activate against the disease, it needs specific information about the structures or cells it must attack. For this purpose, the body has specialized information cells that work as watchmen and present antigens. Their strongest and most important representatives are the dendritic cells. Their task is to collect pieces of malignant or infected cells (called antigens) and to present them to specific immune cells (lymphocytes). With this information, antigen-specific lymphocytes develop mostly into killer or effector cells, which attack and destroy the dangerous cells all over the body. A small portion of these specific lymphocytes become memory cells, which will allow an appropriate immune response in the long term.

A precondition for the immune system to fight the tumour cells is therefore specific information. Only through “antigen presentation” will the lymphocytes be able to recognize and destroy the tumour cells in order to sustain a long-term defence against them.

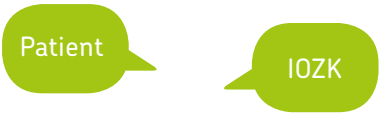
Optimal timing for the treatment

It is best to start the therapy with IO-VAC® immediately after complete removal of the tumour, a process called “R0 resection”. During the operation, a portion of the removed tumour tissue should be used for the immunotherapy and to that end be frozen in sterile and dry conditions to be sent immediately to our specialized laboratory.

> **Usually, our immunotherapy can start at any stage of the disease progression. The sooner it starts, the better are the chances of success, especially with regard to prevention of relapses.**

In cases where the disease is already in an advanced stage, the development of a tumour-specific, cytotoxic immune response should be supported by our vaccine prior to the use of checkpoint inhibitor antibodies. This way, the effect of checkpoint inhibitor therapy is enhanced.

Consultation



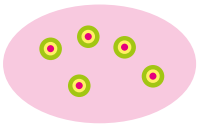
Hospital

Tumour removal operation

Sample of patient's tumour to produce antigens

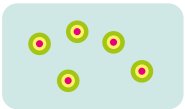
Alternative: Tumour fragments from blood (liquid biopsy)

IOZK Laboratory



Tumour cells primed with ND Virus for lysis

Loading of the dendritic cells and applying the vaccine at a later time



Frozen conservation and storing

Dendritic cells – crucial information carriers

In the immune reaction against cancer, the patient's dendritic cells play a crucial role. Thanks to highly modern cell cultivation technology, they can be produced from a simple blood sample in our laboratories. To this end, a particular group of white blood cells, the monocytes, are isolated from the blood of the patient. In a more complex process, they can be developed into dendritic cells in five to seven days by cultivating them with diverse messenger substances and growth factors.

Their production is regulated by the German Medicines Act (Arzneimittelgesetzgebung or AMG for advanced therapies) and demands time and specialized personnel. It requires a specialized laboratory of the highest quality, strongly equipped and officially admitted for this task. The IOZK produces a personal medication for each patient, which is why this process is bound to bigger costs.

Dendritic cells play a crucial role as the watchmen of our immune system. They are the strongest cells in presenting antigens, activating killer cells and providing a successful immune response. Their name comes from the characteristic tree-like branches (from the Greek “dèndron” = tree).

Loaded with information

The dendritic cells receive the necessary information about the cancer cells while outside the body. Through a specific method, they are confronted in the test tube with dead and especially modified, antigen effective cell proteins of the patient's own tumour, and thus “loaded” with specific information.

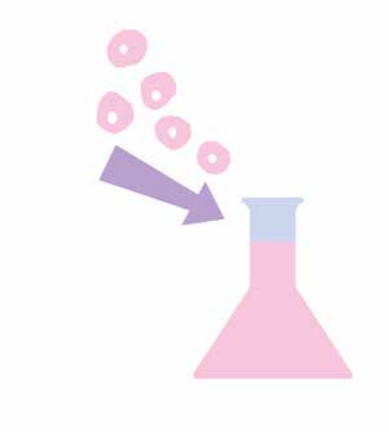
Passing Information

The transmission of information from the dendritic cells to the lymphocytes takes place back inside the patient's body. To this end, the cells cultivated and information loaded in the laboratories, are injected back into the body. Once there, they move into the lymphatic system and pass the information on to the lymphocytes. These are activated through this contact and start fighting the tumour cells all over the body.

A method with nearly no side effects

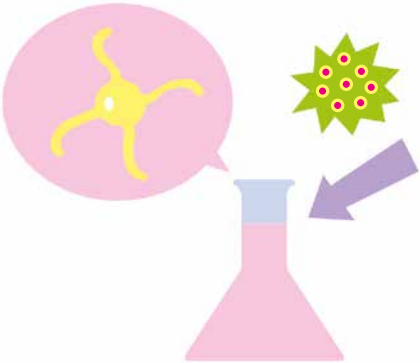
There are no risks involved in injecting the activated information cells that have been in contact with dead tumour cell material. Firstly, it is a vaccine composed of the body's own cells, and secondly, the tumour material was already killed and modified through special processes.

The cell compound is tested for absolute purity and only given to the patient after a thorough molecular analysis – according to the guidelines of the Medicines Act. Several studies have proven this process to be harmless.
It must also be noted that it is a physiologically specific therapy, meaning that it only attacks tumour cells and no healthy cells, therefore producing only minor side effects.



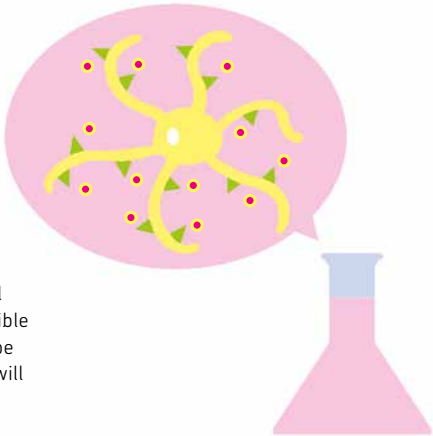
1.

From the blood of the patient, specific white blood cells, known as monocytes, are isolated. These are put in cultivation bottles to develop into dendritic cells through a complex method.



2.

After 5 days: A large number of dendritic cells have developed. Now, they will be loaded with the specific characteristics of cancer cells, the tumour antigens, in combination with the Newcastle disease virus.



3.

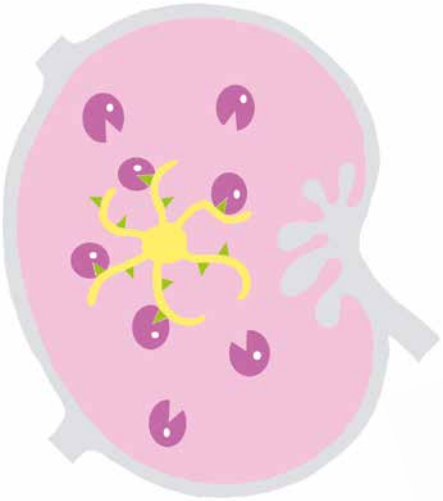
After 7 days: The antigen was decomposed by the cells. Its characteristics are now visible on the surface. The samples in the test tube have developed into dendritic cells, which will help the body to start an effective immune response.

4.

The cell compounds are tested for molecular biological quality and absolute purity. Now the IO-VAC® vaccine compound can be injected.

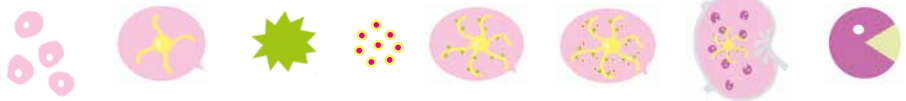
5.

The dendritic cells quickly find their way into the lymphatic system. There they inform the lymphocytes about the surface of the tumour antigen (antigen presentation).



6.

The activated lymphocytes or effector cells have received a clear signal. They reproduce and spread out to realize the defence reaction. Cancer cells that have the antigen infected by the virus are targeted by the immune cells, attacked and destroyed.



Monocytes | Immature dendritic cell | Tumour antigen | Viruses | Mature dendritic cell | Dendritic cell loaded with antigens | Lymphatic knot | Activated T cell

Highest purity and qualification in laboratories

For such a particular and individualized form of therapy, highly qualified professionals are indispensable. The production process abides to the GMP guidelines and takes place inside a cleanroom laboratory, which excludes any factors of interference. In this space, human cells are grown inside a special nutrient fluid at body temperature.

For this reason, the cleanroom needs to have absolute sterility, to prevent the contamination of cell cultures. This is achieved through a system of permanent positive air pressure with air showers for personnel and materials. A continuous outward flow of air prevents impurity from entering the room. Together with high quality machine equipment, these complex facilities ensure strict purity standards.

At the IOZK laboratories, a highly qualified team of professionals works under the guidelines of the European Medicines Act and GMP (Good Manufacturing Practice).

Viruses –
Assistants of the therapy

Once tumour cells manage to survive for a certain time inside the body, they become tolerated by the immune system as part of the body itself, even though as cancer cells they are dangerous to the organism. The T lymphocytes, as part of the white blood cells, are charged with destroying cancer or infected cells, but will not attack structures perceived as part of the body. This tolerance is supposed to protect the body from autoimmune diseases, but in the case of tumour cells becomes paradoxical and detrimental to the organism.

With a smart method, this tolerance of cancer cells can be overcome. There are viruses that infect only tumour cells, whereas healthy cells remain unharmed by them. Among these is the Newcastle disease virus (NDV). It is pathogenic for birds but harmless for humans, whose health remains unaffected. For its use we have received a government permit.

After the virus has penetrated into the tumour cells, it changes them. Once infected, these cells emit “danger signals”, so that the immune system becomes aware of them. Now the immune system can react to these infected tumour cells. This way the tolerance of tumour cells is cancelled.

> **This infection helps the immune system to distinguish the cancer cells from the healthy body cells and to fight them.**

The IOZK fulfils all requirements to work with viruses – in this case the Newcastle disease virus. Samples of the patient's own tumour are combined with the virus and used to load dendritic cells. The IOZK, in cooperation with VALNEVA and GenIBET Biopharmaceuticals, has developed the production of NDV according to the European Pharmacopoeia ad usum humanum (for therapeutic use in humans). Thus, following the German Medicines Act for advanced therapies, the IOZK uses the first Newcastle disease virus produced pharmacologically under GMP in the world, as part of the vaccine compound IO-VAC®.

Questions and answers about the NDV/DC tumour therapy

Why do standardized tumour therapies often not provide the desired success?

Genetic research has made clear that tumours are composed in very different ways. In cases of colon cancer, for example, the tumour-specific molecular structures showed only a minor match between patients.

Each person's cancer is unique. This is why, from the beginning, we decided to use samples of the patient's own tumour. This way we can produce a bespoke and polyvalent vaccine, which will train the immune system against further tumour growth.

Is a patient cured after an R0-resection?

In many cases, individual tumour cells actively move away from the tumour cluster at an early stage. This already takes place before the tumour can be surgically removed or even before it is detected.

Some of these separate cells embed themselves as metastasis initiating cells (MIC) in a part of the body far away from the original tumour. These cells can become active immediately or after some time, and create a metastasis. For this reason, cancer patients frequently fall ill again after a successful tumour removal, in what is termed a recurrence. Our therapy allows to prevent this situation.

Are there alternatives if no tumour sample is available?

Through a special process of liquid biopsy, information about the cancer can be gained from simple blood samples. The liquid biopsy is used by tumour diagnostics to give an early diagnostic or to control an ongoing therapy. At the IOZK, we also use this method of analysis to gain the patient's own tumour antigens in order to produce the vaccine, in case nothing or not enough of the actual tumour is available.

As the tumour grows, small bits of DNA or complete tumour cells drift away from it and move freely through the blood. Liquid biopsy allows the detection of these tumour fragments in the blood. Analyzing the obtained tumour samples enables to deduce, for example, the properties of the tumour, which makes it possible to control and monitor the therapy towards specific goals. In the aftercare, this procedure can also tell whether the tumour was treated effectively or if a relapse of the tumour has occurred.

In order to gain tumour samples from the blood, the tumour, its metastasis or their area, are treated for some days with loco-regional modulate electrohyperthermia, combined with oncolytic virotherapy. This treatment leads to a growing number of exosomes, immunogenic microparticles and apoptotic bodies, which are tiny pieces of tumours and can be harnessed as antigens from a blood sample thanks to a liquid biopsy.

Why do we vaccinate?

The root of a tumour consists of cancer stem cells (CSC) and in later stages also of metastasis inducing tumour cells (MIC). These define the progression of the tumour. They split into tumour cells that keep reproducing and stem cells, which don't reproduce at first, but rest until a potential activation. Nowadays we know that a tumour holds a great variety of mutations among its stem cells. Since these don't split often, they cannot be reached by conventional radiotherapy or chemotherapy. After these therapies end, tumour growth can always start again, in form of metastases or otherwise.

Therefore, the goal is to prevent the growth of metastases. Our immunotherapy focuses on the specifics of tumour cells (including both CSC and MIC) and can develop an immunologic memory. This is based on T cells, which have a long lifetime and can promptly and at any time start a new immune response, as soon as tumour cells threaten to become active in the body again.

FAQ

How does the therapy begin?

In solid tumours, therapy starts with resection. In this case, the surgeon removes the tumour completely out of the healthy tissue. Part of the tumour material is required for our therapy and must be sent aseptic, dry and deep frozen to our laboratories in Cologne. The tumour tissue is used to produce the antigens for the vaccine, since they supply the information about tumour antigens of the patient.

Why is immune function tested prior to the therapy?

Before any immunotherapy, the function of the individual's immune system must be considered. Only when results are available, a treatment can be planed – as long as a complete evaluation promises a successful therapy development.

Why do we make the vaccine from the body's own tumour cells i.e. tumour parts?

The immune system can create a polyvalent immune reaction against many of the structures presented to it. Nevertheless, this reaction does not always match the effective response needed against the tumour, as can be the case with standardized tumour vaccines. Only if the immune system recognizes the patient's own tumour material as a danger within the own body, it can produce a specific and whence effective immune response.

What is particular about the IO-VAC® vaccine?

Our cancer treatment is based on an anti-cancer vaccine which stimulates an individual and polyvalent immune response, leading to a precise attack targeted towards tumour cells. It is unique in as far as it is produced from the cells of the patients themselves and adapted to match their immune system.

With this approach we enable the immune system to recognize and fight the tumour cells anywhere in the body, system-wide. Since we use antigens of the patient's own tumour, we develop a variety of different tumour antigens, which support an individual and polyvalent immune response. Basically, we help patients to help themselves.

How is the process of a vaccine therapy?

The NDV/DC vaccine IO-VAC® contains tumour antigens from the patient's own tumour cells in combination with a virus. In cases of inoperable tumours or metastases, tumour samples can be gained from the blood. This oncolysate or tumour samples from the blood are used to load the patient's own dendritic cells. These are of a crucial importance, in combination with the Newcastle disease virus, since they produce a specific immune response from the T cells against the tumour.

The completed vaccine, composed of dendritic cells loaded with autologous tumour antigens combined with the virus, is injected through the skin of the patient. Then a specific immune response against the tumour can develop and spread throughout the entire body. Blood tests are used to monitor the specific immune response in the laboratory. After several steps of immunisation, it normally takes a few weeks until the desired reaction in the patient's immune system develops.

FAQ

What is the Newcastle disease Virus (NDV)?

In our therapy, we use a particular virus, which in humans can only reproduce in tumour cells and has been known to science for several years. Research has proven that the Newcastle disease virus is harmless to humans and in no way causes diseases or significant unwanted side effects. In humans, the virus reproduces only in tumour cells and not in healthy cells. The latter produce a defensive substance called interferon, which limits the reproduction of the virus in healthy human cells.

Why is a virus used?

Most tumour cells cannot produce enough interferon to stop the reproduction of NDV after an infection. The infected tumour cells are labelled by a viral antigen whereby they can be recognized by the immune system and registered as a threat. Now, tumour cells also present the danger signals emitted by the virus, to which the immune system reacts by starting the destruction of tumour cells.

We make use of the selective viral replication of the Newcastle disease virus, in order to immunologically label the tumour cells. In this way, the immune system can better and faster distinguish the tumour cells from the healthy ones. On top of that, microbiological danger signals as those of viruses increase the effectiveness of a cytotoxic immune reaction.

What can be expected over time?

In the case of an ideal early application, the goal is to sustain the health of our patient. In advanced cases, we seek to relieve the symptoms of the disease and to reach an extension of survival time with high quality of life. In contrast to conventional therapies, the vaccination method with IO-VAC® offers a long term therapy. This means that the effect of the vaccine keeps developing after the application or therapy and remains active on its own.

Are there any side effects?

Unlike chemotherapy, our vaccination method only produces minor side effects. At the beginning of the immunotherapy, more or less strong flu-like symptoms may appear. There are no other known side effects.

What does "individualized therapy" mean?

Tumour-specific immunotherapy is an individual therapy. The immune system is enabled to fight cancer with its own strength through the aid of a vaccine produced from the body itself. This means that each patient receives a therapy especially tailored to their own physical conditions, genetics and symptoms, which must also consider the individual developments and mutations of the tumour.

To this end, the autologous vaccine IO-VAC® is produced according to the European Medicines Act and the Good Manufacturing Practice (GMP) for each single patient as a personal medicine. This way the patients of the IOZK receive the best possible, specific and personally tailored immunotherapy.

FAQ

What is an "individual healing attempt"?

Under German Law, "the individual healing attempt" is part of a medical doctor's therapeutic freedom. It represents a procedure which has the well being of the patient as its priority and for which other therapy options have been exhausted. Alternatively, it can be started earlier by initiative of the patient. It is therefore a form of compassionate use.

In contrast to a clinical trial, the main goal is not to produce data that can be generalized. There are no legal limits for the number of cases. A particular form of this is the "healing attempt series", in which several individual healing attempts are carried out simultaneously or consecutively.

(For further reading: Huber, Fabian, „Individueller Heilversuch und klinisches Experiment“, Inaugural-Dissertation, Juristische Fakultät, Universität Augsburg, 2014.)

What is the legal background?

The use of our vaccine is permitted according to the European Medicines Act on advanced therapy medicinal products (ATMP). It is the first combined vaccine of its kind in Europe.

Several paragraphs of the German Medicines Act need to be considered:

- Authorisation to produce dendritic cells (§13 German Medicines Act for Advanced Therapies)
- Authorisation for processing human cells, i.e., tumour material (§ 13 German Medicines Act for Advanced Therapies / § 20c German Medicines Act)
- Authorisation to work with viruses, i.e., NDV (German Animal Infectious Disease Control Act § 2 / Biological Substances Control Act V)
- Authorisation to produce a tumour antigen through virus infection (§ 13 German Medicines Act for Advanced Therapies / § 20c German Medicines Act / Biological Substances Control Act V)

The IOZK uses the world-wide first NDV produced according to the European Pharmacopoeia for human use under GMP conditions.

The typical development of immunotherapy at the IOZK

Cancer diagnosis

IOZK consultation

Histologic examination of the tumour samples

Immuno-oncologic diagnosis

The typical development of immunotherapy at the IOZK

Operation

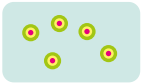
1st IO-VAC® vaccination cycle

8-14 days in Cologne

4 weeks

4 weeks

Hyperthermia



The patient's own tumour antigens are combined with the virus

Alternative:
Tumour fragments from blood (liquid biopsy)

Producing dendritic cells from the patient's blood

Loading with tumour antigens in combination with virus

Immuno-oncologic diagnosis

2nd IO-VAC® vaccination cycle

8–10 days in Cologne

Check

5–7 days in Cologne

Booster

4 weeks

4 weeks

Hyperthermia

Immuno-oncologic diagnosis

Has immunologic memory developed?

In case of metastases, memory cells activate the immune system

Additional “booster” vaccine if necessary.

Specific immunotherapy – a new dimension in the treatment of cancer

In conventional cancer therapy, the treatment focuses on the eradication of the cancer cells through external interventions: surgery, radiation, chemotherapy. More recently antibody therapies and targeted therapies are being used. These are monospecific therapies. Usually solid tumours react to these monotherapies within short time with a mutation, which results in a resistance against the monotherapy. This can add to the explanation why, despite decades of research and years of experience, no satisfactory results have been achieved for many types of cancer.

The fact that the immune system plays a special role has been assumed for a long time. In 1908 Paul Ehrlich together with Ilja Metschnikow received the Nobel Prize for Medicine for the establishment of immunology. Back then, Paul Ehrlich gave a lecture on the relationship between immunity and tumour formation. But only in recent years have the methods been developed for the analysis and manipulation of the immune system. 2010 the first therapeutic tumour vaccine was admitted in the USA, specifically against prostatic carcinoma.

The IOZK uses the active principle for which the Nobel Prize 2011 was awarded:

1. **The presentation of antigens by dendritic cells (DC) (Ralph Steinman)**
2. **The combination with immunogenic danger signals (Jules Hoffmann and Bruce Beutler)**

Only through this combination can a cytotoxic reaction be started.

The leading scientific journal “Science” named cancer immunotherapy as the breakthrough of the year in 2013.

New antibody therapies, like checkpoint inhibitors, are effective even when the tumour is at an advanced stage. These antibody therapies presume an existing immune response against the tumour tissue. The treatment method established by the IOZK, in combination with the autologous vaccine IO-VAC®, for which we received a production license in 2015, creates the platform for the successful use of these new advanced therapy options. The scientists who discovered and described the check point inhibitors received the Nobel Prize in Medicine 2018 for it.

In oncology, polyvalent immunotherapy is not yet a standard. It is generally known that a new scientific idea often takes a generation before it becomes fully accepted. In addition, this type of immunotherapy is absolutely individualized. It is based on the use of the body's own cells and is a time consuming and costly procedure.

> **Clinical studies where the patient's own antigens were used demonstrated a significant increase in survival time.**

As a translational centre, it is the IOZK's mission to put cutting-edge research findings into practice as part of individualized therapies, providing an effective immunotherapy to patients who urgently require our help, even if it is not yet established as the standard treatment for cancer. However, an individualised treatment always requires that the patients actively choose the direction to take and their therapy options.

Research

Clinical studies have shown that specific immune therapies can be combined well with conventional therapies. Furthermore, our therapy with the autologous tumour vaccine IO-VAC® hardly presents any side effects.

For deeper insights into our scientific work, please visit our website:
www.iozk.de/website/publications/en

Interaction with other forms of therapy

The IOZK Immunotherapy considers the interactions with other therapies through their impact on the immune system. For example, we consider the defence mechanism of the tumour in our therapeutic scenario and proceed to any necessary treatments to support the activity of immune cells that fight the tumour. Additionally, interactions of the immune system with other therapies, for example chemotherapy, must be considered.

Not all therapies are compatible with an immunotherapy. The timing and intervals of each therapy must be considered to determine their sequence. These interactions must be calculated individually when planning the therapy.

Not every immune activation is good!

In case of cancer, the immune system should always be activated specifically only against the tumour growth; it must be polarized, so to speak. An immune activation that is not targeted but unspecific can also support immune cells that help tumour growth. As an example of this, one can name regulatory T cells, which protect other cells from the attacks of immune cells, or M2 macrophages, which are responsible for the regeneration of tissue.

Triggering immunogenic cell death (ICD)

The ICD therapy is a supporting immunologic therapy, which can start during chemotherapy. In recent years, several mechanisms of cell death were studied. Since cells in living organisms are constantly renewing themselves, they must adjust to a programmed death in order to give space to new growing cells. This programmed cell death is also called apoptosis. The physical death of cells does not produce any additional reactions.

Tumour cells have the particularity of reproducing faster, but they disregard the programmed cell death and remain in place. This leads to the accumulation of cells in a single place, forming a tumour. Chemotherapies use this cell accumulation. Their elements insert into the cells during their splitting phase, so as to poison them. The resulting cell death normally causes no reaction from the immune system; instead, chemotherapy decreases the effectiveness of the immune system.

With immunological therapies, we can induce an immunological cell death in the tumour. The therapy activates the immune system against tumour growth, even during chemotherapy, by presenting dead tumour cells to the immune system. Under particular circumstances - as during a mild suppression chemotherapy - it is possible to induce cell death through loco-regional modulate electrotherapy and oncolytic virotherapy. Under this supporting measure, the chemotherapy and the timing must be considered when planning the therapy.

> **The goal is to make the immune system take part in the fight against the tumour cells, even during the chemotherapy.**

Without additional toxic side effects, this can optimize the results of the chemotherapy.

Hyperthermia – an ideal additional treatment tool to immunotherapy

Hyperthermia (Greek for “elevated body temperature”) of the entire body, or individual parts of the body, has a variety of desirable effects on the immune system and the tumour cells. It has been used successfully in the treatment of cancer and can improve the effects of the traditional forms of treatment as well as immunotherapy. Depending on the type of cancer and the state of the individual’s immune system, the IOZK applies a variety of methods.

Loco-regional modulated electro hyperthermia

This method is used in cases of minimal tumour growth for outpatient treatment. A therapy session takes up to 60 minutes. Radio waves with a specific frequency are focussed on the tumour from the outside, percutaneously.

> **This method considers the different properties of the tumour cells and healthy cells. As opposed to healthy cells, only the tumour cells take stress and damage from the radio waves.**

To protect themselves from cell death, the tumour cells attempt many things, for example to form heat shock proteins (HSP). But by producing these HSPs, the tumour cells lose their camouflage and can be detected by the immune system. Through an electric field, radiofrequency hyperthermia causes the formation of HSP in the tumour as well as programmed cell death. This results in cell fragments (apoptotic bodies) being formed which can then be caught by immune cells and presented to the immune system.

In addition to the direct effect of the warmth and the electrical field, this form of hyperthermia shows an immunological effect. Furthermore, the elevated temperature causes an increase in blood flow through the tumour that enhances the effectiveness of radiotherapy and/or chemotherapy as well as antibody therapy and virotherapy.

Moderate whole body hyperthermia

This method elevates the body core temperature to between 38.5 and 40.5° C . This corresponds to a natural fever reaction that activates the immune system. The patient rests on a bed in a thermal isolation tent. A layer of warm air forms around the body through infrared radiation and prevents evaporative cooling. Body temperature, heart rate, blood oxygen levels and blood pressure are monitored continuously. This is followed by a resting period. The treatment session can take up to six hours. The aim of whole body hyperthermia is to set the immune system to a state of high alert.

We use whole body hyperthermia as an additional tool for aiding the success of the overall treatment. It improves the tolerance and optimizes the effect of chemotherapy, while also activating the immune system. For each treatment with hyperthermia, we take into consideration each individual patient's condition and immune status.

A new perspective on cancer treatment

The form of our therapy requires an overall new perspective.

Up until now, persons were only considered healthy if they presented no tumour. Many of our patients do live without a tumour, but we also have many long term patients who despite having a tumour of limited size, can live comfortably.

For example, if the tumour grows slowly, it is possible to keep pushing it back. That is our every-day reality in our treatment centre.

Nowadays, a balance between the tumour and the immune system appears to be more important than ever.

The goal is to extend the metastases free survival of our patients, while ensuring a high quality of life. The extension of overall survival in connection to new personalized immunotherapies has been proven by recent data.

Dr. Wilfried Stücker

Pharmaceutical Biology, Translational Oncology, Naturopathic Practitioner

> **"With our multi-disciplinary approach at the IOZK we offer our patients valuable treatment options which supplement and expand conventional methods."**

The insights we have gained in the last decades about the functioning of the immune system play an important role in our work as team of experts. Given the abundance of medical knowledge in today's world, it is essential to collaborate in interdisciplinary networks and to exploit synergies in this way.

This is also the guiding principle of our team at the IOZK. The close cooperation between our medical and scientific experts provides our patients with valuable treatment benefits derived from cutting-edge scientific research. This has resulted in our team developing the first therapeutic autologous polyvalent tumour vaccine based on dendritic cells loaded with virus-infected autologous tumour antigens.

Stefaan Van Gool, MD, PhD

Specialist in Paediatric Hemato-Oncology
Medical Management of Translational Oncology
Responsible Person (European Medicines Act)

Languages:

English
French
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German

> **"Over the last ten years, immune therapy has become a strong fourth pilar for oncology. It is a broad term, composed of passive and active immunization strategies combined with tumour-specific immune modulation therapies."**

In our vision for translational oncology, we now integrate multimodal immune therapy as part of our standard cancer therapy, which can already contribute in establishing a long term immune defense against cancer. Through the combination of anti-cancer strategies with multimodal immune therapy options, we deliver a highly personalized medical approach, which considers the dynamics of the patients' tumour and their body.

Prof. Dr. rer. nat. Volker Schirrmacher

Tumour Immunology, Head of Research

> **"Through the specific activation and individual support of the immune system to fight against a patient's own cancer, new and promising treatment options are available to patients today."**

Overcoming barriers is one of the current challenges in oncology. Only then can we develop innovative therapies. Immunotherapy is a prime example of this new type of treatment in oncology. Successful results have shown us that we are on the right path with our treatment approach.

At the IOZK we offer patient-specific immunotherapy. This way we can quickly and flexibly adapt to the needs of our patients, so that our individual therapy is implemented much better and in a more personal manner than, for example, at a university clinic. We work on the basis of clinical studies that are specifically optimised for the individual patient.

Dr. med. Katharina Sprenger

Specialist in General Medicine, Tumour Immunology
Responsible Person (European Medicines Act)

> **"When treating tumour diseases, it is becoming even more apparent that there is no universal patient and no universal tumour. Standardised procedures that do not take the individual situation into consideration are only of limited benefit."**

I trust that the future of tumour therapy lies in personalised medicine. The guidance and strengthening of the patient's own defence mechanisms – instead of exclusively destroying the tumour through surgery, chemo- and radiation therapy – convinces me. I am delighted that I have the good fortune to be able to work on the development of such strategies to benefit the patient.

Dr. med. Tobias Sprenger

Specialist in General Medicine, Consultant for Expert Medical Opinions

> **"Guidelines should support doctors and patients to find the correct therapy, not replace the thinking process."**

In my profession as a doctor it is of utmost concern to me to understand the values and needs of my patients. It is important to me to recognise them as individuals and support their autonomy. Individuals who consciously select their own mode of therapy and identify with it stand a better chance of overcoming a health crisis than those that blindly leave the treatment decision to somebody else. This is the reason why I distrust medical practice which blindly follows rules and regulations without acknowledging the individual patient.

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Languages:

English

German

Russian

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Glossary

Antigen – Molecular structures, to which antibodies and specific lymphocyte-receptors can bind. Lymphocytes can directly destroy antigens or produce antibodies against them.

Apoptosis – A form of programmed cell death, the “self-destruction program” of individual cells

Autologous – (pertaining to the same individual, matching) The patient's/body's own cells or tissue

Checkpoint inhibitor antibody - Monoclonal antibodies that neutralize blocking molecular structures. This type of antibody therapy can support an immune reaction.

Cytotoxic – A characteristic of substances, viruses or T cells, which can destroy other cells

Cytotoxic immune response - A targeted immune reaction from T cells that produces cell destruction, e.g. special immune cells target and destroy tumour cells

Exosomes - Vesicles (bubles) of about 30 to 90 nm in size which are released from a cell to its environment

Granulocyte – Round immune cells, part of the white blood cells (leucocytes) and of a natural immune response

Immunogenic cell death (ICD) – Any form of cell death produced by an immune response

Leucocytes – White blood cells

Liquid biopsy (LB) – A sampling and analysis of non-solid tissue, mostly blood

Lymphocytes – A subgroup of white blood cells (leucocytes) in the immune system. Among the lymphocytes are B cells, T cells and natural killer cells. They develop in the lymphatic system (bone marrow, lymphatic nodes, spleen, thymus) and fight foreign elements like viruses or modified autologous cells like tumour cells.

Macrophages – White blood cells (leucocytes) and part of the scavenger cells (phagocytes). They play a key role in inflamation and healing and can play a role in supporting tumour growth.

Monocytes – White blood cells of the immune system that destroy viruses and other structures foreign to the body with help of antigen presentation

Multimodal – A form of treatment connecting various forms of procedure that can be adapted to each patient's individual situation

Natural killer cells – Lymphocytes acting cytotoxically i.e. that can not only recognize tumour cells and infected cells, but also destroy them.

Neutrophile granulocytes – Leucocytes that are part of the born immune system and serve as primary defence by identifying and destroying micro-organisms. They are the most common form of white blood cells in humans.

Oncolytic viruses – Viruses that destroy tumour cells directly or indirectly through oncolysis

Phagocytes – Scavenger cells, part of the immune system. They play an important role in the immune response. In this group are the macrophages, the monocytes, the granulocytes and the dendritic cells.

Polyvalent – A vaccine of multiple values, directed against several antigens

Recurrence – Reappearance of a disease or its symptoms

Glossary

Relapse – Reappearance of a disease after temporary cure, mostly related to the reappearance of tumours

T lymphocyte – T cells are important for immune response as they recognize antigens. Together with B lymphocytes, they represent acquired immunity. T is short for thymus, the place where these cells mature after being produced in the bone marrow.

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