PetBioCell

DENDRITISCHE ZELLTHERAPIE
FÜR HUNDE, KATZEN UND PFERDE

Veröffentlichungen

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PetBioCell

Veröffentlichungen zur Dendritischen Zelltherapie

Wir haben für Sie die einzelnen Veröffentlichungen zur dendritischen Zelltherapie aus den letzten Jahren zusammen gestellt. Die Veröffentlichungen wurden auf unterschiedlichen Kongressen in Form von Postern oder Präsentationen vorgestellt und sollen die Anwendungsbereiche und Erfolgschancen anhand von Auswertungen darstellen.

Um die wissenschaftliche Basis der dendritischen Zelltherapie weiter zu stärken, bleiben wir mit allen behandelten Patienten während des gesamten Behandlungsverlaufs und danach weiter in Kontakt. Die Daten, die wir von den Patientenbesitzern und den Tierärzten bekommen, helfen uns, in Zukunft noch bessere Aussagen über die Prognose von Patienten mit unterschiedlichen Tumorerkrankungen zu geben.

Die Erfahrung in den letzten 16 Jahren hat gezeigt, dass die dendritische Zelltherapie eine vielversprechende Behandlungsmöglichkeit für viele Patienten und Patientenbesitzer ist. Bei einigen Tumorarten und Lokalisationen ist zudem die Kombination mit bekannten onkologischen Behandlungsmöglichkeiten interessant.

Unabhängige Studie mit der Kleintierklinik Hofheim

Die durch Dr. Thomas Grammel und PetBioCell gemachten Erfahrungen mit der dendritischen Zelltherapie werden zur Zeit auch von der Kleintierklinik in Hofheim unter der Leitung von Dr. Martin Kessler untersucht. Dabei führt die Kleintierklinik eine placebokontrollierte Studie zum Hämangiosarkom beim Hund durch. Die Patienten werden dabei zufällig in zwei gleichgroße Gruppen eingeteilt. Eine Gruppe erhält ein Placebo und die andere Gruppe bekommt die dendritische Zelltherapie.

Die Kriterien zur Studienteilnahme sind:

- gesicherte histologische Diagnose eines Hämangiosarkoms der Milz
- Keine Bluttransfusion während / nach der OP
- Blutentnahme für die dendritische Zelltherapie nicht später als 14 Tage nach der OP
- Es dürfen keine Metastasen nachgewiesen sein
- Es darf keine Chemotherapie durchgeführt werden
- Die Hälfte der Patienten bekommt zufällig zugeteilt ein Placebo zur Kontrolle
- Regelmäßige Kontrolluntersuchungen zur Bewertung des Patienten

Wenn Sie einen Patienten haben, der diese Kriterien erfüllt, melden Sie sich bitte schnellstmöglich nach Erhalt des Befundes bei der Tierklinik Hofheim

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oder direkt bei PetBioCell.

Veröffentlichungen zur Dendritischen Zelltherapie

Die folgenden Veröffentlichungen wurden bereits zu unterschiedlichen Themen auf einschlägigen Kongressen und Fachzeitschriften veröffentlicht.

K. Penner, T. Hawacker, T. Grammel (2019) - Immunologic Treatment of intraocular melanoma after enucleation to avoid metastatic melanoma, ESVO Meeting, October 3 - 6 2019, Dun Laoghaire, Dublin, Ireland

B. Müller, M. Grammel, T. Grammel (2019) - Treatment of a recurring corneal hemangiosarcoma in a horse with a combined photodynamic diode laser therapy and a dendritic cell therapy, ESVO Meeting, October 3 - 6 2019, Dun Laoghaire, Dublin, Ireland

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T. Grammel, T. Hawacker, H. Hettling, S. Grammel (2019) - Quality of Life of dogs during immunologic treatment with monocyte-derived dendritic cells, 25th FECAVA EuroCongress, St. Petersburg, Russia, September 2019

Dr. Thomas Grammel (2017) - A Pilot uncontrolled study of postsurgical treatment with autologous dendritic cell-based immunologic therapy in 17 dogs with mammary adenocarcinoma

C. Arnold, I. Dreher, T. Grammel, G.F. Schusser (2017) - Immunotherapy of a squamous cell carcinoma in the perianal region using autologous dendritic cells in a horse, Equine Veterinary Education

Dr. Tina Hawacker (2016) - Tumortherapie mit autologen dendritischen Zellen, BERNER Fortbildung Onkologie: Innovative Ansätze und Arbeitsschutz, Hamburg, 7. Dezember 2016

Elisabeth Pötzsch (2016) - Immunologische Behandlung des caninen Hämangiosarkoms der Milz, Jahrestagung des Arbeitkreises Vakzine der DGfI, Göttingen, 7. November 2016

Dr. Thomas Grammel (2016) -Tumortherapie mit autologen dendritischen Zellen, BERNER Fortbildung Onkologie: Innovative Ansätze und Arbeitsschutz, Hamburg, 12. Oktober 2016

Dr. Thomas Grammel (2016) Plattenepithelkarzinom - Immunologische Behandlung beim Pferd, HundKatzePferd 06/2016, 24-27

Dr. Thomas Grammel (2016) - A Pilot uncontrolled study of postsurgical treatment with autologous dendritic cell-based immunologic therapy in 10 dogs with splenic hemangiosarcoma, 3rd World Veterinary Cancer Congress, Foz do Iguassu/ Brazil May 25-29,2016

Dr. Corinna Arnold, Dettmer-Richardt, C. (2016) Therapie eines Plattenepithelkarzinoms der Haut – moderne Behandlungsansätze, Vortrag Leipziger Tierärztetag, 16.1.2016

Dr. Thomas Grammel (2015) – Immediate immunologic treatment following cytoreducton in fibrosarcoma of cats, Poster, VCS conference, Tysons, VA USA

Dr. Thomas Grammel (2015) – A Pilot, uncontrolled study of postsurgical treatment with autologous dendritic cell-based immunologic therapy in 20 cats with fibrosarcoma, Poster, ISFM Congress, Porto, Portugal

Dr. Thomas Grammel (2015) – Immunologic Therapy with Monocyte-derived Dendritic Cells in Canine Liposarcoma, Presentation, World Veterinary Congress, Istanbul, Turkey

Dr. Thomas Grammel (2015) – Quality of Life of Cancer Patients Treated with Dendritic Cell Therapy, Presentation, World Veterinary Congress, Istanbul, Turkey

Ina Dreher (2015) – Immunologic Treatment with Dendritic Cells in Equine Squamous Cell Carcinoma, Presentation, World Veterinary Congress, Istanbul, Turkey

Dr. Thomas Grammel (2014) – Canine Melanoma Treated with Autologous Dendritic Cell-Based Vaccines in 10 dogs, Presentation, ESVONC Congress, Vienna, Austria

Dr. Thomas Grammel (2014) – From rural veterinary practice to specialized immunological laboratory, Presentation, American Animal Hospital Association, Nashville, TN, USA

Dr. Thomas Grammel (2014) – Prime Time for Autologous Dendritic Cell Vaccines – Poster, Veterinary Cancer Society, Mid-Year Conference, Asheville, NC, USA

Dr. Thomas Grammel (2013) – Post-Surgical Treatment with Monocyte-Derived Dendritic Cell Vaccines in Dogs and Cats, Presentation, 1st World Veterinary Congress, Prague, Czech Republic, 17-20 September 2013

Dr. Thomas Grammel, Dr. Claudia Dettmer-Richardt (2013) – Dendritische Zellen in der Tumortherapie, HundKatzePferd 8/2013, S. 12-14.

Dr. Thomas Grammel (2012) – Don't Hesitate to Vaccinate Immunotherapy with Dendritic Cells – 2 Case Studies, Poster, Veterinary Society of Surgical Oncology, Fort Collins, Colorado, USA, May 24-25

Dr. Thomas Grammel, Dr. Elisabeth Müller (2007) – Immuntherapie bei Tieren mit dendritischen Zellen, Poster, SVK Jahrestagung, Montreux, Switzerland

Quality of Life of dogs during immunologic treatment with monocyte-derived dendritic cells
Poster,
25th FECAVA EuroCongress, St. Petersburg, Russia, September 2019

1. Introduction

Tumor treatment with monocyte-derived dendritic cell vaccines is used as a part of the overall effort in oncologic treatment. For the owner the question of qualitiy of life for his dog and possible side effects of a therapy are an important part of decision making. For other treatment options in onologic patients studies about qualtiy of life under treatment were already published.

2. Methodology

To learn more about these parameters owners of diseased dogs were asked to answer a questionaire. 555 questionaires could be evaluated for this study. The questions were identical for the medical and health situation of the dog in the week before and the week post dendritic cell treatment. Questions involved overall health, medication, exercise and exercise time, need for rest, pain expression, food intake, anorexia, incontinence, gastrointestinal signs.

3. Results

These results were compared between ante and post treatment and showed: The overall health status improved significantly, the same finding is true for quality of life. The dogs showed more exercise time and needed less pain medication. The owners experienced subjectively already a better qualitiy of life because the dogs were less listless, showed less clinical signs and saw better qualitiy of life (longer exercise time).

4. Discussion

Immunologic treatment is a treatment option which shows a quick positive reponse in the health status and qualtity of life of dogs treated.

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Quality of Life of dogs during immunologic treatment with monocyte-derived dendritic cells

25th FECAVA EuroCongress, St. Petersburg, Russia

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Introduction

Tumor treatment with monocyte-derived dendritic cell therapy is used as part of the overall effort in oncologic treatment. For the owner, the question of **qualitiy of life** for his dog and **possible side effects of a therapy** are an **important part of decision making**. For other treatment options in onologic patients, studies about quality of life during the treatment are already published (e.g. chemotherapy).

Methodology

To learn more about these parameters, owners of diseased dogs treated with dendritic cell therapy were asked to answer a questionnaire. 656 questionnaires could be evaluated for this study. The questions were identical for the medical and health situation of the dog in the **week before and the week post dendritic cell treatment**. Questions involved overall health, medication, exercise and exercise time, need for rest, pain expression, food intake, anorexia, incontinence, gastrointestinal signs.

Results

The results were compared between ante and post injection of the dendritic cell therapy and showed: **The overall health status in dogs improved significantly, the same is true for the quality of life.** The dogs showed more exercise time and needed less pain medication. The owners experienced subjectively already a better qualitiy of life because the dogs were less listless, showed less clinical signs and saw better qualitiy of life (longer exercise time).

Discussion

The dendritic cell therapy as an immunologic treatment is a treatment option which shows a quick positive reponse in the health status and qualtity of life of dogs treated.

Data

Overall, there were 656 questionnaires answered. For some patients, the evaluation was done for multiple subsequent applications with dendritic cell therapy.

Questionnaires	1x	2x	3x	4x	5x	6x	7x	Total
# of observations	221	67	60	11	9	3	2	656

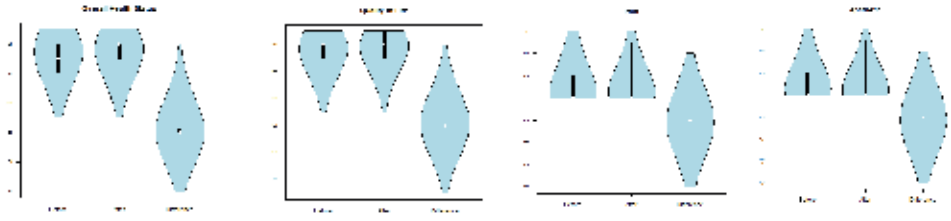
	Mean before	Mean after	Relative deviation	P-Value
Overall health status[1]	5.166	5.355	3.66 %	0.014
Overall quality of life[1]	5.416	5.640	4.14 %	0.002
Physical Effort[2]	1.978	1.932	-2.33 %	0.382
Going for a walk[2]	1.976	1.986	0.51 %	0.867
Impression of pain[2]	1.618	1.522	-5.93 %	0.049
Medication[3]	0.285	0.325	14.04 %	0.119
Panting[2]	1.961	1.943	-0.92 %	0.726
Poor appetite[2]	1.322	1.330	0.61 %	0.854
Help eating / defecating[2]	1.132	1.141	0.80 %	0.754
Urine leakage / diarrhoea[2]	1.296	1.298	0.15 %	0.947
Nausea / Vomiting[2]	1.188	1.206	1.52 %	0.553
Apathetic[2]	1.535	1.433	-6.64 %	0.020

[1] The scale is 1 = "very bad", 7 = "excellent".
[2] The scale is 1 = "not at all", 2 = "few," 3 = "moderate", 4 = "very / a lot"
[3] The scale is 0 = no, 1 = yes

Items of the Questionnaire

Evaluated before and after the injection of dendritic cells.

- Overall health status
- Overall quality of life
- Does your animal have difficulties with physical effort / movement?
- Does your animal have difficulties going for a walk?
- Do you have the impression that your animal has pain?
- Do you give your animal medication against the pain?
- Does your animal pant a lot?
- Does your animal have a poor appetite?
- Does your animal need help with eating or defecation / urinating?
- Does your animal have urine leakage / diarrhoea?
- Does your animal suffer nausea or vomiting?
- Is your animal apathetic?



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Quality of Life of Cancer Patients Treated with Dendritic Cell Therapy, Presentation, World Veterinary Congress, Turkey, Istanbul, 2015

1. Introduction

For cancer patients, often the quality of life is more important than a complete remission of the tumor. Traditional treatment approaches such as chemotherapy or radiation therapy are often immunosuppressive and induce unwanted side effects leading to a deterioration of the quality of life of the patient. Especially in situations where a curative treatment may not be possible, using these treatments means that the patients' quality of life is reduced for the limited time the patient still has. Furthermore, the owner often asks for a treatment which maintains or improves the quality of life for the patient instead of focusing on life expectancy. This analysis should show that immunotherapy can successfully be used to improve the quality of life of the patient.

2. Methodology

Using a standardized questionnaire, patients receiving dendritic cell therapy were evaluated by their owners. This main goal of this investigation was to find side effects of the treatment and give the owners a way to communicate if any undesired effects occurred during the treatment.

With each treatment, the pet owner received a survey asking to evaluate the quality of life and possible side effects of the treatment. This survey should give the pet owner the possibility to give us (and the veterinarian) feedback about possible side effects, deterioration or improvements of the patient's health during the treatment. The pet owners were asked to fill out the questionnaire in the week after the application, therefore evaluating the situation right before the treatment and after the treatment. At no cost, the pet owner could send back the questionnaire in a provided envelope.

3. Analysis

For this analysis, responses from 87 patients with 129 observations have been evaluated. Since pet owners receive a survey with each treatment, multiple observations per patient are possible.

Table 1 shows the frequency distribution of the observations. Most of the patients only have one observation, some have 2 and very few have more than 2. Since most of the patients received at least 3 treatments at the beginning of the therapy, this clearly shows that the willingness to participate in the survey decreases over time (with each subsequent treatment). This may be due to no changes in the observation (same as before) or because nothing "drastic" has to be reported. "The patient is fine".

4. Results

Overall Health Status

Question asked: How would you evaluate the overall health status of your patient? The data shows that **the overall health status of the patients is increasing in the week after the treatment**. The mean over all patients increases by 4.66% from 4.799 to 5.209 (p=0.164) (from 7 possible points). This improvement is especially present in dogs where the overall health status increases by 8.63% from 5.051 to 5.487 points (p=0.03). The small p-value indicates, that this improvement is statistically significant.

The black bar in the figure in the graph for "differences" underlines these findings: The tendency of differences (before and after) is clearly positive (above zero), indicating that there are almost no patients where the overall health status is decreasing.

Quality of Life

The week after the treatment (injection of dendritic cell therapy), the patients' quality of life improves by 4.29% from 5.248 to 5.473 points (p=0.166) (7 being the highest possible quality of life). Especially, dogs show an improvement of quality of life of 6.44% from 5.372 to 5.718 points (p=0.056). Again, the tendency of differences (before and after) is clearly positive (above zero), indicating that there are almost no patients where the quality of life is decreasing.

Quality of Life of dogs during immunologic treatment with monocyte-derived dendritic cells
Poster,
FECAVA Congress, St. Petersburg, 2019

1. Introduction

Tumor treatment with monocyte-derived dendritic cell vaccines is used as a part of the overall effort in oncologic treatment. For the owner the question of qualitiy of life for his dog and possible side effects of a therapy are an important part of decision making. For other treatment options in onologic patients studies about qualtiy of life under treatment were already published.

2. Material & Methods

To learn more about these parameters owners of diseased dogs were asked to answer a questionaire. 555 questionaires could be evaluated for this study. The questions were identical for the medical and health situation of the dog in the week before and the week post dendritic cell treatment. Questions involved overall health, medication, exercise and exercise time, need for rest, pain expression, food intake, anorexia, incontinence, gastrointestinal signs.

3. Results

These results were compared between ante and post treatment and showed: The overall health status improved significantly, the same finding is true for quality of life. The dogs showed more exercise time and needed less pain medication. The owners experienced subjectively already a better qualitiy of life because the dogs were less listless, showed less clinical signs and saw better qualitiy of life (longer exercise time).

4. Conclusion

Immunologic treatment is a treatment option which shows a quick positive reponse in the health status and qualtity of life of dogs treated.

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Canine Melanoma Treated with Autologous Dendritic Cell-Based Vaccines in 10 Dogs, Presentation, ESVONC Congress, Vienna Austria

1. Introduction

The presented research shows the result of an autologous dendritic cell-based cancer treatment in 10 dogs suffering from malignant melanoma in various localizations. The autologous production of dendritic cells and the ability to present autologous antigens to the immune system yields very good clinical results.

2. Material & Methods

Through gradient centrifugation and a adherence step, a monocyte culture is extracted from the fresh whole blood of the patient. These monocytes are then cultivated with specific cytokines in order to derive autologous DCs. Finally, the DCs are primed with autologous tumor lysate. The antigen presenting DCs are then harvested, resuspended and injected intradermal in the patient.

3. Results

10 dogs have been treated with dendritic cell-based cancer vaccines. Median survival time is 785 days after the initial treatment with DC vaccine. Survival rate after 446 days is 66,7% and after 830 days still 40%, remaining constant until the end of the observation period. Due to the fact that 4 of the 10 patients are still alive, the censored result is preliminary and subject to further improvement.

4. Conclusion

Independent of localization (oral mucosa and different skin localizations), the expected longevity of the patients increased. Together with surgical excision of the cancer cells, the application of DC-based vaccines yields promising results in the treatment of malignant melanoma in dogs, also in rather difficult localizations such as the oral mucosa. Additionally, since no or very slight side effects could be observed, the quality of life of the patients was maintained.

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A Pilot, Uncontrolled Study of Postsurgical Treatment with Autologous Dendritic Cell-Based Immunologic Therapy in 10 Dogs with splenic hemangiosarcoma, Presentation, 3rd World Veterinary Cancer Congress, Foz do Iguazu, Brazil

1. Introduction

This sesarch shows the result of an autologous dendritic cell-based cancer treatment in 10 dogs suffering from splenic hemangiosarcoma. The production of autologous dendritic cells (DCs) and the ability to present autologous and tumor specific antigens to the immune system yielded promising clinical results.

2. Material & Methods

The dogs showed hemascus and were undergoing an emergency surgical laparotomy, removal of tumor particles and splenectomy. If the result of the following pathohistological confirmed a hemangiosarcoma, the immunologic treatment was immediately started. A fresh whole blood sample from the patient was processed by gradient centrifugation, followed by adherence steps to derive the patients' monocytes. These monocytes were cultivated with specific cytokines to derive autologous DCs. The culturing lasted for 7 days. The cells were then harvested unprimed, resuspended and injected intradermally. The basic protocol consists of three treatments every 4 weeks with newly cultivated DCs. 10 dogs were treated using this protocol and the median survival time was 611 days after treatment with DC therapy. The survival rate after 365 days was 71% and after 730 days was 57%. Patients shoud receive DC-based immunologic re-treatment immediately post-surgery and an interval of 4 to 6 month of re-treatments life-ling is recommended.

3. Results

DC-based immunologic treatment of canince splenic hemangiosarcoma bears interesting positive results in longevity of the patients.
In this study, surgical excision followed by DC-based therapy yielded promising results in the treatment of splenic hemangiosarcoma of dogs with no or mild side effects. However, further results from controlled studies are now required to investigate and confirm any potential efficacy of the DC-based vaccine therapy.

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Immunologic Therapy with Monocyte-derived Dendritic Cells in Canine Liposarcoma
Presentation
World Veterinary Congress, Istanbul, Turkey, 2015

1. Introduction

The standard treatment of canine liposarcoma is typically restricted to a surgical reduction of the tumor mass, since a prolonged survival time after an additional postsurgical management with radiation or chemo therapy is not common. In this abstract, the postsurgical treatment using dendritic cell therapy in three dogs with liposarcoma is presented as an additional treatment option.

2. Material & Methods

Three male dogs were treated. A 9-year-old French Bulldog was pre-treated with surgery and radiation but had a recurrence of liposarcoma. A 3-year-old Irish Wolfhound mix and a 7-year-old Australian Shepherd had no prior treatment after pathological-histological diagnosis of liposarcoma.
All dogs underwent tumor mass reducing surgery prior to the immunologic treatment, but no clean margin surgery was achieved.
Immediately after surgery, the dogs were treated with primed dendritic cells derived from the patient's own monocytes. Autologous tumor lysate was used for priming. The cell suspension was applied intradermally.

3. Results

All dogs showed a positive immunologic reaction. After the second application in a cycle of three applications every four weeks, a very distinct demarcation and fistula-formation was observed in the area of the surgical site. Additionally, the quality of the patients' lives has been improved.

4. Conclusion

The immunologic treatment with dendritic cells shows promising effects in canine liposarcoma after incomplete surgical resection.

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Immunologic Treatment of intraocular melanoma after enucleation to avoid metastatic melanoma
Poster
ESVO Meeting October 3 - 6 2019 Dun Laoghaire, Dublin, Ireland

1. Introduction

Two dogs underwent an enucleation because of a malign process in the posterior section of the eye. The pathologist reported no clean margins in the histological sections. To avoid metastatic disease the dendritic cell therapy was started soon after the surgery.

2. Material & Methods

1ml whole blood per kg of body weight was taken from the dogs. Following a centrifugation and adherence phase a monocyte fraction was obtained. These monocytes were cultivated in a cleanroom environment with canine cytokines (GM-CSF and IL-4) to derive autologous DCs. The treatment was carried out three times in a monthly interval after renewed blood sampling and cell preparation of the monocytes. The treatment was administered at two anatomical sites: locally in the area of the surgical field and intradermal in the inguinal area.

3. Results

The dogs live more than three years after enucleation without any sign of recurrence or metastasis of the melanoma.

4. Conclusion

Immunological treatment with dendritic cells derived from monocytes can prevent recurrence/metastasis of ocular melanoma. Therefore, such a therapy should be considered for malignant eye diseases after enucleation.

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Immunologic Treatment of intraocular melanoma after enucleation to avoid metastatic melanoma

ESVO Meeting
October 3 - 6 2019
Dun Laoghaire,
Dublin, Ireland

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Purpose

Two dogs underwent an enucleation because of a malign process in the posterior section of the eye. The pathologist reported no clean margins in the histological sections. To avoid metastatic disease the dendritic cell therapy was started soon after the surgery.

Material/method

1ml whole blood per kg of body weight was taken from the dogs. Following a centrifugation and adherence phase a monocyte fraction was obtained. These monocytes were cultivated in a cleanroom environment with canine cytokines (GM-CSF and IL-4) to derive autologous DCs. The treatment was carried out three times in a monthly interval after renewed blood sampling and cell preparation of the monocytes. The treatment was administered at three anatomical sites: **locally in the area of the surgical field, intradermal in the area of the mandibular lymph nodes and the axillary lymph nodes**.

Results

The dogs live more than two years after enucleation without any sign of recurrence or metastasis of the melanoma.

Discussion

Immunological treatment with dendritic cells derived from monocytes can prevent recurrence/ metastasis of ocular melanoma. Therefore, such a therapy should be considered for malignant eye diseases after enucleation.

Procedure Dog 1

Crossbreed, female, 15 years, 5.6 kg

Date	Milestone	Day
06.09.17	Surgery	0
26.09.17	1st Application	20
25.10.17	2nd Application	49
17.11.17	3rd Application	72
28.08.19	Follow-up	721

Recommended initial treatment

Procedure Dog 2

Crossbreed, female, 9 years, 15 kg

Date	Milestone	Day
16.02.16	Surgery	0
07.04.16	1st Application	51
26.04.16	2nd Application	70
01.09.16	3rd Application	198
27.10.16	4th Application	254
04.05.17	5th Application	443
01.09.17	6th Application	563
01.02.18	7th Application	716
12.07.18	8th Application	877
17.01.19	9th Application	1066
02.08.19	10th Application	1263
28.08.19	Follow-up	1289

Dog 1 before surgery

Dog 2 before surgery

Dog 2 after surgery

Recommended treatment procedure

- Day 0 — Surgery
- Day 7 — 1st Application with DCs
- Day 35 — 2nd Application with DCs
- Day 86 — 3rd Application with DCs
- Every 150 days — Follow-up treatments with DCs

Literature

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A Pilot Uncontrolled Study of Postsurgical Treatment with Autologous Dendritic Cell-Based Immunologic Therapy in 17 Dogs With Mammary Adenocarcinoma

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Introduction

This poster shows the result of an autologous dendritic cell-based cancer treatment in 17 dogs suffering from mammary adenocarcinoma.

Canine mammary tumors are the most common type of neoplasia in middle-aged female dogs. Approximately half of these neoplasias are malignant and of these 50 % carry significant metastatic potential (1). Adenocarcinomas are tumors of epithelium of glandular origin, in these cases of mammary tissue. They infiltrate surrounding tissue, are locally aggressive and metastasize hematogenous or lymphogenic to distant sites including the lungs, liver, bone, and often the skin (2,3).

Therapy concepts in mammary tumors include aggressive surgery, radiation therapy and chemotherapy, also as a multimodal combination therapy (4,5).

Hormonal therapy through spaying of young bitches is regarded as an important element in the prevention of mammary cancer.

As Dendritic cells (DC's) possess very potent antigen-presenting abilities, they serve as an attractive cell-type for cancer vaccine strategies (6,7). Through the research of Steinman and Peters (8,9,10,11), this therapeutic approach became available. In veterinary medicine, immunologic treatments with DC's are used since the 2000's (12,13,14,15). This work presents the therapeutic use of dendritic cell therapy in the treatment of mammary adenocarcinoma in female dogs.

Material & Methods

Excision of the tumor tissue was used to reduce the tumor burden for all dogs: The dogs were undergoing lumpectomy or mastectomy. A fresh whole blood sample from the patient was processed by gradient centrifugation and an adherence step to derive a population of the patients monocytes. These monocytes were cultivated with specific cytokines (GM-CSF and IL-4) to derive autologous DCs. The DC's were cultured for 7 days.

On the final day, the DCs were harvested, re-suspended and injected intradermal into the area of the patient's tumor site.

Treatment Plan

1. Surgery of lump / mammectomy, lymph node
2. Wait for Patho-histology
3. Immediately after malign diagnosis: Start of DC-Treatment
4. Initial cycle with three applications, each 4 weeks apart.
5. Subsequent applications in a 3 month interval.

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Results

The immunologic treatment for 17 dogs using this protocol started between 2010 and 2015. The medium age of the bitches at start was 9.1 years. The following breeds were present: eight mixed breed, three Golden Retriever, two Poodle, and one Border Collie, Australian Shepherd, Kangal and Dachshund. The presented data is **censored** as 11 dogs are still living (01Sep2017). Two dogs died of lung metastases (euthanized) (219/537 days post start of DC treatment), one because of disease unrelated epilepsy (245 days), three because of age (526-1828 days).

The **censored median survival time was 895 days after the first treatment with DC therapy**. The survival rate after 1 year was 88% and after 2 years 76%.

Independent of the anatomic site and size of the adenocarcinoma, the expected longevity of the patients undergoing a DC treatment increases. In this study, surgical excision followed by DC-based therapy yielded **promising results in the treatment of mammary adenocarcinoma** in dogs with no side effects as seen with other therapies. However, further results from controlled studies are now required to investigate and confirm the potential efficacy of the DC-based therapy.

This may be done also in the light of enhanced quality of life and longevity of the patients and as an easy and comfortable treatment option for owner and home veterinarian without hazardous substances.

Implication

In order to achieve an optimal treatment result, we suggest the following treatment plan:

1. **Best possible tumor resection to reduce the tumor burden.**
2. **Perform patho-histology analysis.**
3. **In case of a malign patho-histological diagnosis - immediately start with DC-therapy.**
4. **Initial treatment cycle with three applications, each four weeks apart.**
5. **Subsequent applications in a 3 month interval.**

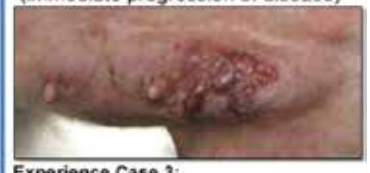
Case 1: Partial or total mastectomy
(**Typical** situation)

Experience Case 1:
- **High percentage** curative,
- No recurrence of disease
- No metastatic disease
- Normal life span
- Very good quality of life

Case 2: Surgery not possible
(Other underlying diseases, i.e. Age of animal, size of tumor burden)

Experience Case 2:
- Palliative successful
- Shrinking of tumor burden
- Metastatic disease
- Prolonged life span
- Good quality of life

Case 3: Skin metastases
(immediate progression of disease)



Experience Case 3:
- No immunologic treatment recommended

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Immediate immunologic treatment following cytoreduction in fibrosarcoma of cats
Poster
isfm Congress Porto, 2015

1. Introduction

Since more than a decade monocyte-derived dendritic cell vaccines are used in the treatment of feline fibrosarcoma. This is a first study of this immunologic approach with this therapy produced in a GMP-controlled laboratory.

2. Methods

11 cats were treated with an immunologic treatment of monocyte-derived dendritic cells that were primed with tumor-tissue of the animal's fibrosarcomous cells at different time intervals post surgery.

3. Results

11 cats with fibrosarocma which were treated with a monocyte-derived dendritic cell after tumorreduction showed depending on the onset of the first treatment a different outcome: 5 cats treated immediately post surgery are still without recurrence of disease (median 598 days post op, 454 - 833 days), the group of 6 cats treated not until at least 5 weeks post surgery had only a median survival time of 199 (67 - 557) days. All cats of group 2 have already died.

4. Conclusion

Immediate postsurgical immunologic treatment with primed dendritic cells seems to be an effective treatment in feline fibrosarcoma and leading to prolonged survival times compared to established therapy options.

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VCS Annual Conference
Vienna, VA Oct 15-17, 2015

Introduction

Feline fibrosarcomas originate from mesenchymal cells or fibroblasts. They evolve from skin, subcutaneous tissue, or oral cavity and infiltrate surrounding tissues, are locally aggressive and metastasize hematogeneously to distant sites including the lungs, liver, bone, brain and skin (1,2,3).

The main therapy concepts in feline fibrosarcoma are aggressive surgery, radiation therapy and chemotherapy (3), also as a multimodal combination therapy (4). Furthermore, surgical excision and electrochemotherapy (5) or immunotherapy using recombinant viruses expressing interleukin-2 (IL-2) (6) are reported as treatment options.

Dendritic cells (DCs) possess very potent antigen-presenting abilities and are an attractive target for cancer vaccine strategies (7). This treatment approach started in human medicine in the 1970's and 1980's with the fundamental research of Steinman and Peters (8,9,10,11). In veterinary medicine, DCs are used since more than a decade (12,13,14,15,16). In this presentation, the application of DC therapy in 11 cats with feline fibrosarcoma is presented.

Material & Methods

Radical excision of the tumor tissue was used to reduce the tumor burden in 5 of the 11 cats. A fresh whole blood sample from the patient was processed. Monocytes were isolated by gradient centrifugation and an adherence step. These cells were cultivated with the cytokines GM-CSF and IL-4 for 6 days to develop DCs. In 5 of the 11 cats, the culture was primed with autologous tumor lysate on day 5. The next day, the DCs were harvested, resuspended and injected intradermally around the tumor site. In the cases of unprimed DCs, treatments were injected directly into the tumor and at another body site intradermally.

	Unprimed (6 cats)	Primed (5 cats)
Median age	11 y	8,4 y
Time Span Post surgery (median) until treatment	1 y (35d - 780d)	Treatment immediately post-sugery
Survival (median)	199d (67d - 557d)	645d (489d - 848d)
Still alive (Oct. 1, 2015)	0/6	5/5

Results & Implication

11 cats were treated using primed or unprimed dendritic cells developed under GMP-conditions. The median age of the cats was 10.1 years. The **median survival time differed considerably between the two groups.**

The immediate postsurgical use of DC-Therapy is mandatory for a successful treatment of feline fibrosarcoma.

In order to achieve an optimal result, the best possible tumor resection to reduce the tumor burden should be carried out. Quickly followed by the start of a DC-therapy. Because of the aggressive nature of the feline fibrosarcoma – also in the case of a recurrence – the following immunologic treatment scheme is successfully used:

3 treatments in a monthly interval following a three-month treatment interval.

If the patient stays free of recurrence, a longer interval is introduced.

For every treatment, a new blood sample is taken. At least 5 ml of full blood are needed to start the procedure.

The tumor lysate is portioned after processing and stored deep frozen to be reused for following treatment cycles. When the tumor lysate is used up, unprimed treatments are performed to support the immune system.

Case – unprimed DCs

Suzie, 18 y old female castrated cat, carries a big (fibrosarcoma) tumor burden around the hind back since a long time. She is an example for a palliative use of the DCs. Repeated surgery with regrowth. The owner asked for a DC treatment to let the tumor size shrink. The unprimed DCs were administered into two sites: (1) directly into the tumor tissue and (2) intradermally. Already 5 days after the DC therapy, the tumor wall opened and tumor tissue and liquid leaked out of the wound. The tumor volume shrank drastically. She was feeling very comfortable beside the constantly draining tumor site. Only local cleansing and disinfection was used. (The shown example is a new case and not yet included in statistics.)

Prior treatment (June 2015)

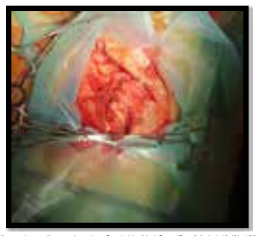
August 2015

Case – primed DCs

Susi, 7 y, wk ESH, was presented with a spherical fibrosarcoma of 10 - 12 cm diameter, that was undermining the skin and penetrating the abdominal wall into the abdominal cavity on the right loin. Susi underwent immediate surgery, the tumor was removed and the abdominal wall reconstructed without trying to get clean margins. Already at the day of the surgical intervention, blood was drawn and processed for a DC treatment. 6 days post surgery, the first treatment with DCs followed, application was intradermal. The wound healed primarily. Stitches were taken out after 10 days. The DC treatment was repeated after one and two months. In September 2015, the cat is in a healthy condition, no recurrence of the fibrosarcoma or of a metastasis was noticed.

Pre-Surgery Jan 2, 2014

Surgical Site - intraabdominal tumor bed



Intradermal Application of DC Jan 8. 2014

Wound Feb 4, 2014

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A Pilot, Uncontrolled study of postsurgical Treatment with autologous dendritic cell-based immunologic therapy in 20 cats with Fibrosarcoma
Poster
ISFM Congress, Porto, Portugal, 2015

1. Introduction

This research shows the result of an autologous dendritic cell-based cancer treatment in 20 cats suffering from malignant fibrosarcoma in various localizations. The production of autologous dendritic cells and the ability to present autologous and tumor specific antigens to the immune system yielded promising clinical results.

2. Material & Methods

Radical excision of the tumor tissue was used to reduce the tumor burden for all cats. A fresh whole blood sample from the patient was processed by gradient centrifugation and an adherence step to derive a population of patient monocytes. These monocytes were cultivated with specific cytokines to derive autologous DCs. The DCs were then cultured for 6 days and primed with autologous tumor lysate on day 5. The next day, the antigen presenting DCs were harvested, resuspended and injected intradermally and into the tumor site area of the patient.

3. Results

20 cats were treated using this protocol and the median survival time was 448 days after treatment with DC vaccine. The survival rate after 330 days was 58% and after 499 days was 32%. In some patients there was a delay between surgery and receiving the DC-based cancer vaccine and thus it is possible these results can be further improved.

4. Conclusion

Independent of the site of the fibrosarcoma, the expected longevity of the patients appeared to increase. In this study, surgical excision followed by DC-based therapy yielded promising results in the treatment of fibrosarcoma in cats with no or mild side effects. However, further results from controlled studies are now required to investigate and confirm any potential efficacy of the DC-based vaccine therapy.

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A Pilot, Uncontrolled Study of Postsurgical Treatment with Autologous Dendritic Cell-Based Immunologic Therapy in 20 Cats with Fibrosarcoma

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Introduction

This research shows the result of an autologous dendritic cell-based cancer treatment in 20 cats suffering from malignant fibrosarcoma in various localizations.

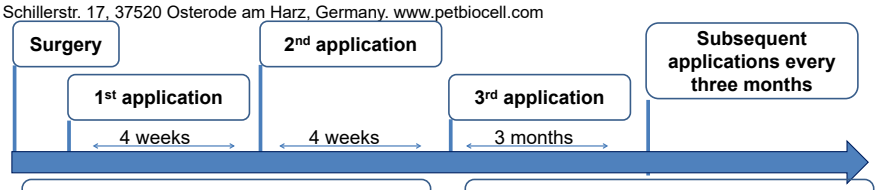
Fibrosarcomas are tumors derived from mesenchymal cells or fibroblasts. Arising from the skin, subcutaneous tissue, or oral cavity they infiltrate surrounding tissues, are locally aggressive and metastasize hematogenously to distant sites including the lungs, liver, bone, brain and skin (1,2,3).

Therapy concepts in feline fibrosarcomas are aggressive surgery, radiation therapy and chemotherapy (3), also as a multimodal combination therapy (4). Furthermore, surgical excision and electrochemotherapy (5) or immunotherapy using recombinant viruses expressing interleukin-2 (IL2) (6) are used as treatment options.

Dendritic cells (DC's) possess very potent antigen-presenting abilities and are an attractive target for cancer vaccine strategies (7). This treatment approach started in human medicine after the groundbreaking discovery of Steinman and Peters (8,9,10,11). In veterinary medicine DC's are used since more than a decade (12,13,14,15). In this presentation the use of dendritic cell therapy in treatment of feline fibrosarcoma is presented.

Material & Methods

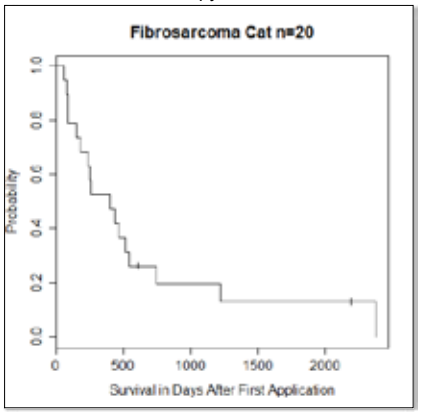
Radical excision of the tumor tissue was used to reduce the tumor burden for all cats. A fresh whole blood sample from the patient was processed by gradient centrifugation and an adherence step to derive a population of patient monocytes. These monocytes were cultivated with specific cytokines (GM-CSF and IL-4) to derive autologous DCs. The DCs were then cultured for 6 days and primed with autologous tumor lysate on day 5. The next day the antigen presenting DCs were harvested, resuspended and injected intradermal and into the area of the patient's tumor site.



Results

20 cats were treated using this protocol and the **median survival time was 448 days after the first treatment with DC therapy**. The survival rate after 330 days was 58% and after 499 days was 32%. In some patients there was a delay between surgery and receiving the DC-based cancer therapy and thus it is possible these results can be further improved.

Independent of the site of the fibrosarcoma, the expected longevity of the patients undergoing a DC treatment appeared to increase. In this study, surgical excision followed by DC-based therapy yielded promising results in the treatment of fibrosarcoma in cats with no or mild side effects. However, further results from controlled studies are now required to investigate and confirm any potential efficacy of the DC-based therapy.



Implication

Postsurgical Use of DC-Therapy:

In order to achieve an optimal result, the best possible tumor resection to reduce the tumor burden should be carried out. Quickly followed by the start of DC-therapy. Because of the aggressive nature of the feline fibrosarcoma – also in the case of a recurrence – the following immunologic treatment scheme is successfully used:

3 treatments in a monthly interval following a three-month treatment interval.

If the patient stays free of recurrence, a longer interval is introduced.

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15. Grammel T. (2014) - Canine Melanoma Treated with Autologous Dendritic Cell-Based Vaccines in 10 dogs, Presentation, ESVONC Congress Vienna May 22-25

Case – primed DCs

Susi, 7 y, wk ESH was presented with a spherical fibrosarcoma of 10 - 12 cm diameter, that was undermining the skin and penetrating the abdominal wall into the abdominal cavity on the right loin. Susi underwent an immediate surgery, the tumor was removed and the abdominal wall reconstructed without trying to get clean margins. At the day of the surgical intervention already blood was drawn and processed in the clean room laboratory. 6 days post surgery the first treatment with dendritic cells followed intradermal. The wound healed primarily. Stitches were taken out after 10 days. The DC treatment was repeated after one and two months.

In June 2015 the cat is in a healthy condition, no recurrence of the fibrosarcoma or of a metastasis was noticed.

Pre-Surgery Jan 2, 2014 **Surgical Site - intraabdominal tumor bed** **Intradermal Application of DC Jan 8. 2014** **Wound Feb 4, 2014**




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Immunotherapy of a squamous cell carcinoma in the perianal region using autologous dendritic cells in a horse
Article
Equine Veterinary Education, 2017

Summary

A 23-year-old Trakehner mare was referred to the Department of Large Animal Medicine with an ulcerative cleft tumour dorsal of the anus and in poor body condition. An infiltrative growing squamous cell carcinoma (SCC) was diagnosed. Surgical treatment was not an option because of the tumour localisation and topical chemotherapy caused severe side effects (coprostasis), therefore an immunological therapeutic approach involving autologous monocyte-derived dendritic cells (DC) presenting tumour antigen on their surface was chosen. Dendritic cells were administered to the patient three times at intervals of four weeks to induce an immune response against the SCC. The tumour regressed in size, the ulcerated surface healed, body condition improved and coprostasis subsided. Six and a half months later small papillomatous neoplasms at the tumour scar led to a fourth treatment. During follow-up, those recurrences remained indifferent; the mare showed physiological behaviour and returned to leisure riding. This case report describes the effectiveness of so far infrequently described immunotherapy with DC in horses.

https://onlinelibrary.wiley.com/doi/abs/10.1111/eve.12741

Treatment of a recurring corneal hemangiosarcoma in a horse with a combined photodynamic diode laser therapy and a dendritic cell therapy
Poster
ESVO Meeting October 3 - 6 2019 Dun Laoghaire, Dublin, Ireland

1. Introduction

A hemangiosarcoma located at the temporal limbus of the right eye, in a 9 year old male castrated warm blood horse was removed by keratectomy in a standing procedure, followed by an immediate photodynamic diode laser therapy. No clean margins were achieved and a recurrence occurred after 16 days.

2. Material & Methods

After a recurrence occurred, the dendritic cell (dc) therapy was added to the treatment scheme in order to prevent the enucleation:

1. Autologous Dendritic Cell Therapy: 3 cycles of DCs which were derived from autologous monocytes and differentiated by GM-CSF and IL-4. The DCs were administered into the conjunctiva palpebralis (1ml) and intradermal into the neck (4ml).
2. Continuing photodynamic therapy with diode laser: Injection of Emundo® 6 cycles between 1.5 and 2 Watt coagulated for 30 sec each, together with the first application of DCs. Subsequently, a renewed laser treatment was omitted and only DCs were injected.

3. Results

47 days after initiating this treatment scheme, the recurrence vanished except for a 1x1 mm small red dot in the episclera, 2 mm behind the limbus. A mild corneal lipid degeneration was still visible. At a follow-up examination 200 days after initiating the treatment, the eye showed no pathological changes anymore, the small red dot was gone.

4. Conclusion

Corneal hemangiosarcomas are difficult to treat (no clean margins, inevitable enucleation), new treatment approaches are necessary.
This case demonstrates that the effect of the photodynamic laser therapy can be enhanced by the dendritic cell therapy in order to avoid recurrence (15 months up to date) in corneal hemangiosarcoma.

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Treatment of a recurring corneal hemangiosarcoma in a horse with a combined photodynamic diode laser therapy and a dendritic cell therapy

ESVO Meeting
October 3 - 6 2019
Dun Laoghaire,
Dublin, Ireland

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Purpose

A hemangiosarcoma located at the **temporal limbus** of the right eye, in a 9 year old male castrated warm blood horse was **removed by keratectomy** in a standing procedure, **followed by an immediate photodynamic diode laser therapy**. **No clean margins** were achieved and **a recurrence occurred after 16 days**.

Material/method

After a recurrence occurred, the dendritic cell (dc) therapy was added to the treatment scheme in order to prevent the enucleation:

1. Autologous Dendritic Cell Therapy: 3 cycles of DCs which were derived from **autologous monocytes and differentiated by GM-CSF and IL-4**. The DCs were administered into the conjunctiva palpebralis (1ml) and intradermal into the neck (4ml).
2. **Continuing photodynamic therapy with diode laser**: intratumoral injection of Emundo®, coagulation in 6 cycles between 1,5 and 2 Watt for 30 seconds each, together with the first application of DCs. Subsequently, a renewed laser treatment was omitted and only DCs were injected.

Results

47 days after initiating this treatment scheme, **the recurrence vanished except for a 1x1 mm small red dot in the episclera**, 2 mm behind the limbus. A mild corneal lipid degeneration was still visible. At a follow-up examination **200 days after initiating the treatment, the eye showed no pathological changes anymore**, the small red dot was gone.

Discussion

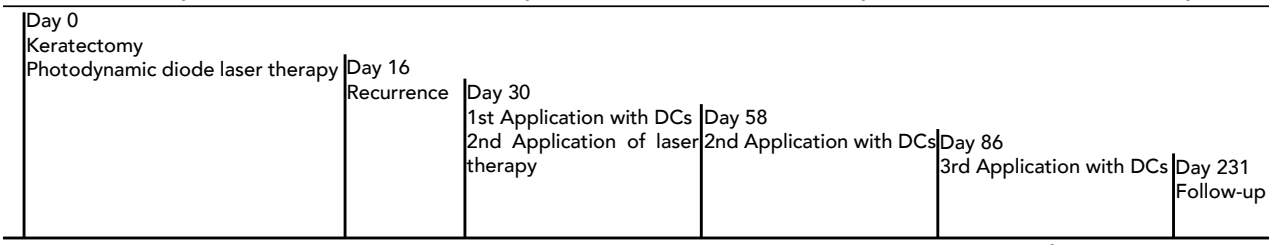
Corneal hemangiosarcomas are difficult to treat (no clean margins, recurrence frequently), new treatment approaches are necessary.
This case demonstrates that the effect of the photodynamic laser therapy can be enhanced by the dendritic cell therapy in order to avoid recurrence (15 months up to date) in corneal hemangiosarcoma.


Day 0


Day 21


Day 86


Day 231



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