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RESEARCH ARTICLE

Dendritic Cell Therapy in the palliative Treatment of Pancreatic Cancer Patients. Experience in 200 Patients

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ABSTRACT

Purpose: Despite improved diagnostic and therapeutic facilities median survival in pancreatic cancer is still unsatisfactory Here we retrospectively analyzed the outcome of immunotherapy in the additional palliative treatment of pancreatic cancer with long antigen exposition dendritic cell therapy (LANEX-DC®) in 200 patients who were treated at our institution (intent-to- treat-analysis).

Patients: Data were available of 200 patients.The mean interval between first diagnosis and start of treatment was 1,5 months. 148 patients received one cycle of dendritic cell therapy, 52 patients received 2 or more cycles of dendritic cell therapy.

Results: Therapy was well tolerated and no serious side effects were observed. The survival rate after 6 months was 70,9 % and afters 9 month 51,0%. The median survival time according to Kaplan- Meier regression analysis was 9,1 months. Median survival was significantly higher in the group of patients who started immunotherapy within 1,5 months following diagnosis (7,9 months versus11,8 months, p=0,009). Patients with two or more cycles of dendritic cell therapy lived significantly longer than patients with just one cycle (17,5 months versus 7,4 months, p=0,001). Interestingly younger patients < 65 years of age lived significantly longer as patients >= 65 years of age (p = 0,004).

Conclusion: We were able to demonstrate in a large retrospective cohort analysis that additional treatment with dendritic cells is highly effective and extends the median survival times up to 17,5 months in case of regular repetition of dendritic cell therapy. Furthermore, we were able to demonstrate that median survival can be increased by early beginning dendritic cell therapy.

Keywords: pancreatic cancer, palliative, immunotherapy, dendritic cells, LANEX-DC®

INTRODUCTION

Pancreatic cancer is the fourth leading cause of death from cancer in the United States in 2010[1]. Gemcitabine has been the standard of care and the only therapeutic option in patients with metastatic pancreatic cancer for years. The benefit of gemcitabine treated patients in stage IV pancreatic cancer was very limited with 5.65 months[2]. Subsequent phase II and phase III studies that aimed to improve the outcome of gemcitabine in combination with different compounds over gemcitabine monotherapy failed except one study gemcitabine with erlotinib, a potent and selective epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor, revealed a statistically, albeit clinically not really meaningful benefit of 0.33 months[3]. However, patients that developed a skin rash showed a hitherto unknown extension of overall survival with up to 11 months[4]. This association has been confirmed in subsequent studies. In 2011 and 2013 data of two phase III studies were released showing a statistically relevant and clinically meaningful improvement in the overall survival of mPC patients thus providing two first line chemotherapeutic options. The PRODIGE-4/ACCORD-11 trial investigated the benefits of therapy with FOLFIRINOX compared with gemcitabine. In this study the treatment with FOLFIRINOX achieved an objective response rate of approximately 31.6% and a median overall survival of 11.1 versus 6.8 months in the gemcitabine mono cohort[5]. These data were very encouraging demonstrating for the first time not only a nearly doubling of the overall survival, but also high objective response rates. Anyhow, it has to be noted that in this PRODIGE trial a highly selective patient cohort was chosen with patients included who were under an age of 76 years with an ECOG of 0 or 1, sufficient renal and liver function (bilirubin up to <1.5 of the norm), a bone marrow with a granulocyte count of ≥1,500 mm^2 as well as a plated count of ≥100,000 mm^2. In a less highly selective patient cohort the MPACT trial investigated the effects of a chemotherapy with gemcitabine/nab-paclitaxel compared with gemcitabine alone. The objective response rate for gemcitabine/nab-paclitaxel was 23% and the median overall survival 8.5 months[6]. The MPACT trial included older patients in slightly reduced general condition. As expected, due to the potent combination of drugs in these regimens, more toxicities like hematotoxicity and polyneuropathy were registered. In general, the FOLFIRINOX regimen showed a higher side effect rate than gemcitabine/nab-paclitaxel with the exception of polyneuropathy which occurred more frequently in the treatment with gemcitabine/ nab-paclitaxel. For review see[7].

Dendritic cells (DC) are the most potent antigen-presenting cells in the body, presenting tumor antigens to T lymphocytes and inducing anti-tumor immune response[8]. Several studies have indicated that dendritic cell therapy is effective in the palliative treatment of different types of cancer[9]. In recent publications it has been indicated that additional dendritic cell therapy for stage 4 carcinoma of the pancreas might improve median survival rates[10,11]. We have recently reported about the beneficial effects of dendritic cell therapy using DC in the additional palliative treatment of patients suffering from pancreatic cancer[12] and the treatment of patients with stage 4 colorectal cancer[13]. In the following retrospective analysis, we update the outcome of palliative additional immunotherapy with DC (LANEX-DC® - long antigen exposition dendritic cells) in patients with pancreatic cancer.

PATIENTS & METHODS

Patients

200 patients suffering from pancreatic cancer that were treated in the palliative situation have been treated with autologous dendritic cells at our institution. The mean age was 63,7 years (31 to 87,1 years). 116 patients were male, 84 patients were female. 58 patients had a recurrence of pancreatic cancer following resection, in 142 patients the tumor was primarily unresectable.The main metastazation sites were liver (65%), peritoneum (28,5%), lung (8,5%), and bones (3%). In 26 patients (13%) the tumor was localized without distant metastazation.

179/200 (88,5%) of the patients received palliative chemotherapy: 133/200 (61,5%) patients received Gemcitabine monotherapy, 8/200 (4%) Gemcitabine plus Oxaliplatin, 11/200 (5,5%) Gemcitabine plus nab-paclitaxel, 7/200 (3,5%) 5-FU and 18/200 (9%) received FolFIrinOx. 2/200 (1%) received transarterial chemoembolization. Patient selections by performance status, liver-enzyme values, etc. were not made.

Immunotherapy with DC was carried out in a median of 1,5 months following diagnosis. Per patient a mean number of 1,5 cycles of DC-therapy was performed (range: 1 – 11 cycles). OS was calculated from the begin of dendritic cell therapy. All of the patients gave a written informed consent for additional treatment with LANEX-DC®.

Generation of mature antigen-loaded monocyte-derived dendritic cells

The whole procedure for gaining the mature dendritic cells was performed according to Good Manufacturing Practice standards (Certificate of GMP compliance DE_BW_01_GMP_2021_0171). Dendritic cells (long antigen exposition dendritic cells) were produced as described recently[13]:

Peripheral blood mononuclear cells (PBMCs) were isolated from 150-200 ml of heparinized venous blood of the patient by density gradient centrifugation (Biocoll®, Biochrom, Germany). PBMCs were seeded in 6-well-plates (BD Falcon, Heidelberg, Germany), and after 2 hours the non-adherent cells were removed. Adherent cells were cultured in RPMI 1640 (Sigma-Aldrich, Munich, Germany) supplemented with 10% of the patient's serum and 2mM L-glutamine (all Sigma-Aldrich, Munich, Germany) in the presence of 750 U/ml rh-GM-CSF and 500 U/ml rh-IL-4 (both CellGenix, Freiburg, Germany) for 7 days. On day 4, media was removed and non-adherent cells were collected from the old media by centrifugation and resuspended in fresh RPMI 1640 supplemented with 10% serum. Again, 750 U/ml rh-GM-CSF, and 500 U/ml rh-IL-4 were added. Maturation of moDCs was induced by adding 20 ng/ml rh-IL-1β, 20 ng/ml rh-TNF-α and 60 ng/ml rh-IL-6 (all CellGenix, Freiburg, Germany). After 24 hours, moDCs were harvested, washed twice in sterile PBS, and an aliquot of the cells was removed for phenotypic analysis and sterility testing. moDCs for immediate vaccination (day 7 of treatment protocol) were resuspended in 1ml sterile saline solution containing 10% autologous serum and administered by intradermal injection in the abdominal cutis. To avoid loss of activity by freezing/thawing the DC were always given directly after production was completed.

Statistical Analysis

Kaplan-Meier estimates were computed using MedCalc®software.

RESULTS

A total of 200 patients with unresectable pancreatic cancer were treated with dendritic cell therapy. Except light flue-like symptoms at the day of reinjection of the dendritic cells in a minority of patients (WHO I/II) no serious side effects were observed, as also reported previously[12-14]. For evaluation of response data of 195 patients were assessed: 3 month after therapy 86 among the 195 patients (44,1%) showed stable disease. In 34 patients partial response was achieved (17,4%) and 75 patients had progressive disease (38,5%). No case of complete response was observed.

Survival was determined from the beginning of dendritic cell therapy. The survival rate after 6 months was 70,9 % and afters 9 month 51,0%. After 12 months 37,4 % of the patients and after 18 months 19,8 % of the patients were still alive.The median survival time according to Kaplan- Meier regression analysis was 9,1 months from start of dendritic cell therapy and 13 months from first diagnosis of pancreatic cancer (fig. 1, tab.1).

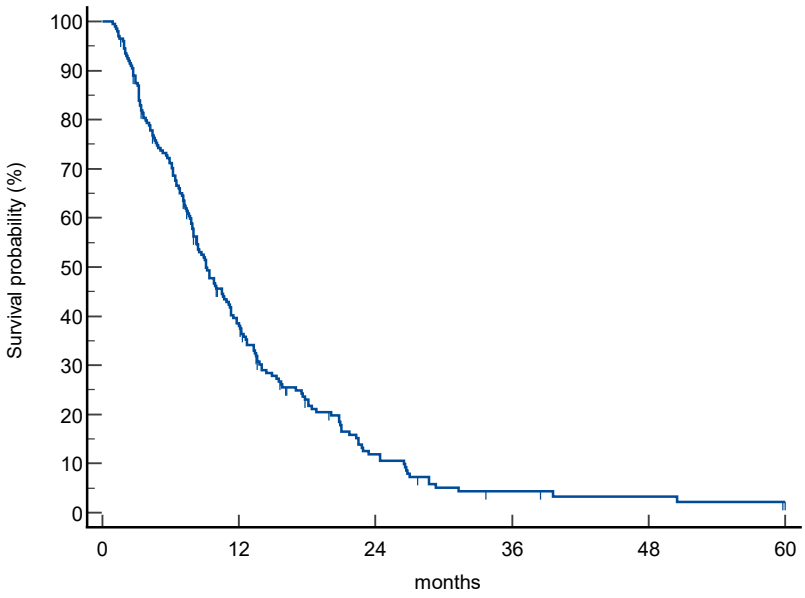

Fig.1: Kaplan-Meier survival analysis of advanced pancreatic cancer patients (n=200) treated with dendritic cell therapy. The overall median survival time was 9,1months

Table 1: Subgroup analyses of palliatively treated pancreatic cancer patients receiving additional dendritic cell therapy. Patients age >= 65 years showed a significantly shorter median survival than patients aged < 65 years. Patients who started dendritic cell therapy within 1,5 following diagnosis lived significantly longer than patients who started dendritic cell therapy more than 1,5 month following diagnosis. Median survival in patients with >= 2 cycles of dendritic cell therapy was significantly higher than in patients with one cycles of dendritic cell therapy.

	no of patients	median survival (months)	significance
All patients	200	9,1	
Gender			
Female	84	11,2	
Male	116	8,3	p = 0,068
Age at diagnosis			
age < 65	103	10	
age >= 65	97	8,3	**p = 0,0046**
Relapse status			
Yes	58	11,3	
No	142	8,5	p = 0,225
Tumor			
Localized	26	10,5	
Metastasized	174	8,7	p = 0,178
Time between first diagnosis and start DC-treatment			
< 1,5 months	99	11,8	
>= 1,5 months	101	7,9	**p = 0,0096**
Chemotherapeutic regimen			
no chemotherapy	21	7,4	
Gemcitabine	133	9,1	
FOLFIRINOX	18	12,1	
nab-Paxlitacel + Gemcitabine	11	6,8	all not significant
Number of cycles LANEX-DC			
1	148	7,4	
> 1	52	17,5	**p < 0,001**

Comparison of different chemotherapies: 21 patients refused chemotherapy with a median survival of 7,4 months. 133 patients received gemcitabine monotherapy, 11 patients nab-paxlitacel plus gemcitabine and 18 patients FolFIrinOx with median survival of 9,1 months, 6,8 months and 12,1 months respectively (not significant, tab.1).

Early beginning of dendritic cell treatment following diagnosis increases median survival significantly: Patients (n=99) who started dendritic cell therapy within 1,5 months following diagnosis lived significantly longer than patients (n=101) who underwent dendritic cell therapy later than 1,5 months following diagnosis (11,8 months versus 7,9 months, p = 0,0096, tab.1). The Kaplan-Meier-Analysis is shown in Fig. 2.

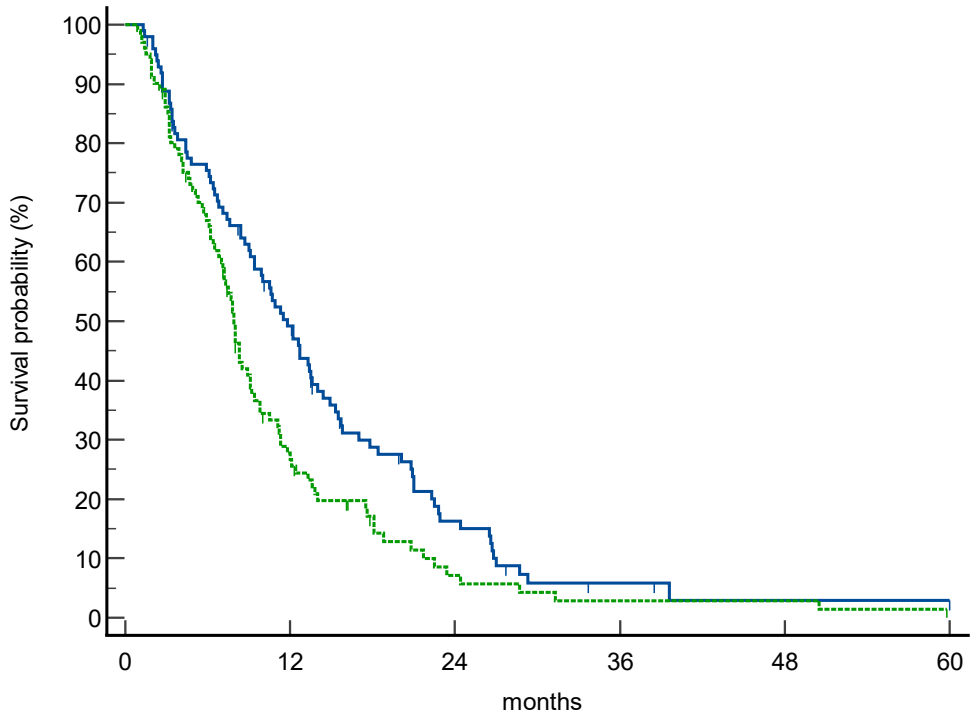

Fig. 2. Kaplan-Meier survival analysis of advanced pancreatic cancer patients (n=200) treated with LANEX-DC®. Patients who started LANEX-DC® therapy within 1,5 months following diagnosis (n= 99) lived significantly longer than patients (n=101) who underwent LANEX-DC® treatment later than 1,5 months following diagnosis (11,8 months versus 7,9 months; p = 0,0096)

Repetition of dendritic cell therapy increases survival significantly: The group of 148 patients who received one cycle of dendritic cell therapy showed a median survival of 7,5 months whereas the group of patients receiving more than one cycle of dendritic cell therapy (n=52, mean number of cycles: 2,73 (range 2 - 11) showed a median survival of 17,5 months (p = 0,0001, tab.1, fig.3a).

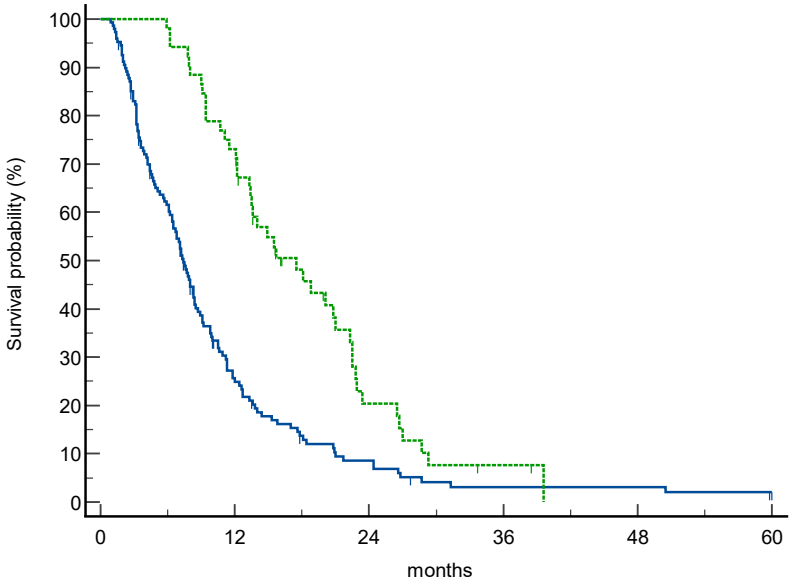

Fig. 3a: Kaplan-Meier survival analysis of patients who had 1 cycle of LANEX-DC® (n=148, solid line) and patients who had >= 2 cycles of dendritic cell therapy (n=53, dotted line). Patients who repeated dendritic cell therapy treatment lived significantly longer than those with a single cycle of dendritic cell therapy (17,5 months versus 7,4 months; p > 0,0001)

The same analysis reduced to the patients who survived at least 5,7 months, the point of time when the first patient who received more than one cycle of dendritic cell therapy died, showed similar results: The group of patients with one cycle dendritic cell therapy (n=90) showed a median survival of 10,6 months as compared to the group of patients who received more than one cycle of dendritic cell therapy (n=52, median survival 17,5 months) (p=0,0076). The Kaplan-Meier analysis is shown in Fig. 3b.

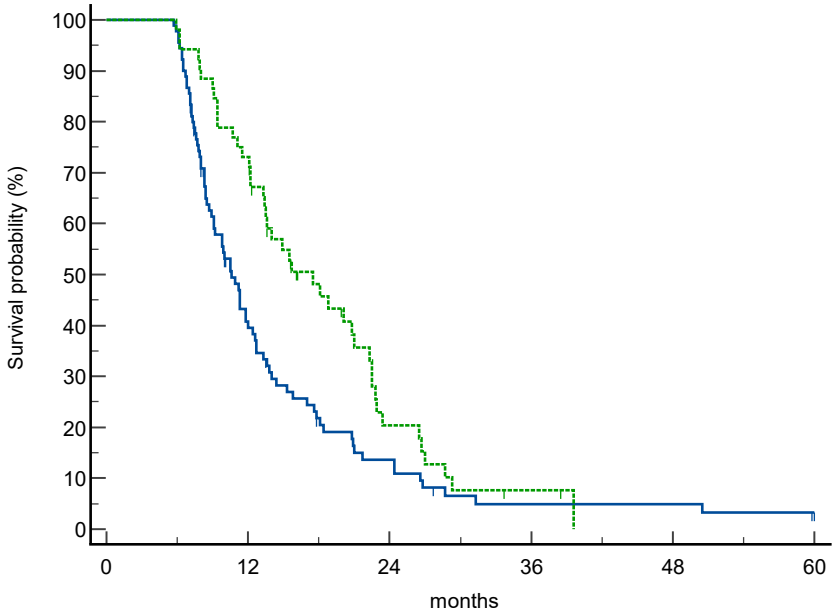

Fig. 3b: Kaplan-Meier survival analysis of patients who surviverdat least 5,7 months. Patients who had 1 cycle of dendritic cell therapy (n=90, solid line) and patients who had >= 2 cycles of dendritic cell therapy (n=53, dotted line). Patients who repeated LANEX-DC® treatment lived significantly longer than those with a single cycle of dendritic cell therapy(17,5 months versus 10,6 months; p > 0,001)

Influence of UICC stage and relapse-status: 26 patients were classified UICC stage 4a, 174 patients were classified UICC stage 4b. There was no statistical significant difference in the median survival between UICC stage 4a (10,5 moths) and UICC stage 4b (8,7 months) (p = 0,178, tab.1). Patients having recurrence following resection of pancreatic cancer (n=58) had a median survival of 11,3 months as compared to a median survival time of 8,7 months in patients without prior resection of pancreatic cancer (n=142) (p = 0,225, tab. 1).

Influence of gender and age : In total 84 of the patients were female, 116 of the patients were male. Although it did not reach statistical significance, there was a tendency, that females lived longer (11,2 months) as compared to males (8,3 months) (p = 0,063, tab.1). Interestingly, younger patients < 65 years of age (n = 103, median survival time: 10,0 months) lived significantly longer as patients >= 65 years of age (n = 97, median survival time: 8,3 months) (p = 0,0046, tab.1).

DISCUSSION

In this retrospective analysis we evaluated the clinical results of 200 patients suffering from pancreatic carcinoma, who were treated with dendritic cells. As many tumours do not elicit a sufficient immune response, which may be due to the reduced function of the immune system or especially to the absence of functional dendritic cells, vaccination with ex vivo generated dendritic cells may overcome this lack[15,16].

Clinically we could observe 17,4% partial responses and 44,1% of the patients showed stable disease. The survival rates were 70,9% after 6 months and 19,8 % after 18 months. The median survival according to Kaplan-Meier regression analysis was 9,1 months. These data are consistent with the series of 134 pancreatic cancer patients published previously[12]. Considering the advanced stages of the disease and the relatively long interval between diagnosis and start of dendritic cell therapy (mean 1,5 months) in the 200 patients we evaluated and taking into consideration, that the vast majority of our patients received gemcitabine monotherapy, the median survival rates seem to be

superior to those achieved with gemcitabine or combinations of gemcitabine[3,4,6]. In our series only 18 patients received FolFIrinOx chemotherapy with a median survival of 12,1 months which is slightly higher than in the group of patients receiving gemcitabine chemotherapy (median survival: 9,1 months) although this did not reach statistical significance. Anyhow, since our group of patients were not selected, comparison of these data should be compared with real world data, as reviewed by Blomstrand et al.[17], showing median survival in gemcitabine treated patients between 4,2 to 6,6 months in real-world cohort analyses[18-20] as compared to our patients who received gemcitabine monotherapy (n=133) plus additional dendritic cell therapy with a median survival of 9,1 months.

In addition, the quality of life was very high, without serious side effects, making it necessary to stay in hospital. Interestingly the younger patients (< 65 years) had even more benefit than older patients (>=65 years) although it is well known from the clinical experience that younger patients have lower median survival times than older patients[21]. A possible explanation for this phenomenon could be that immunological responses are higher in younger patients than in older ones, underlying the effectivity of dendritic cell therapy.

So far, several studies concerning dendritic cell therapy in pancreatic cancer exist, showing an improved survival, most in the combination with chemotherapy[22-30]. An overview is given in Table 2, showing the promising results of dendritic cell therapy in over 560 patients. It is noteworthy that in the big series from Kobayasi[11] patients received five times or more dendritic cells. In our analysis patients receiving more than one cycle of dendritic cells lived significantly longer than patients who only received one cycle of dendritic cells, pointing to a regular repetition of dendritic cell therapy.

Table 2: Comparison of reports of dendritic cell therapy in the palliative treatment of pancreatic cancer. All reports showed an increased median survival as compared to standard treatment.

Author	Year	Patients (n)	Med. Survival (Months)
Kaneko et al.	2005	28	15,8
Nakamura et al.	2009	17	9
Bauer et al.	2011	12	10,5
Kimura et al.	2011	49	11,9
Kobayasi et al.	2014	255	9,9
Gansauge one cycle dedritic cell therapy	2022	148	7,4
> one cycle dendritic cell therapy	2022	52	17,5

CONCLUSION

In conclusion we were able to confirm our data published 2013 concerning additional dendritic cell therapy in the palliative treatment of pancreatic cancer. Our data provide evidence that dendritic cell therapy using LANEX-DC® prolongs median survival in pancreatic cancer. Our analysis further show, that dendritic cell therapy should be started soon after diagnosis and that regular repetition of dendritic cell therapy are beneficial for patients' outcome.

CONFLICT OF INTEREST:

Frank Gansauge is the production manager and joint owner of the laboratory LDG GmbH, where dendritic cells (LANEX-DC®) were produced.

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