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Additional Long Antigen Exposition Dendritic Cell Therapy (LANEX-DC®) in the Palliative Treatment of Stage IV Colorectal Cancer Patients

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Abstract

Introduction: Despite improved chemotherapeutic approaches stage IV Colorectal Cancer (CRC) still has a poor prognosis with 5-year survival rates below 10 percent and a median overall survival below 20 months. Here we retrospectively analyzed the outcome of immunotherapy in the additional adjuvant treatment of stage IV CRC with Long Antigen Exposition Dendritic Cell therapy (LANEX-DC®) in 73 patients who were treated at our surgical department.

Patients: Data were available of 73 patients. Dendritic cells (LANEX-DC®) were produced according to a recently published protocol.

Results: Therapy was well tolerated and no serious side effects were observed. Three year survival and five year survival were 38.7% and 23.3% respectively. The median survival time was 27.8 months.

Conclusion: We were able to show in a cohort of patients that additional treatment with dendritic cells (LANEX-DC®) is highly effective and increase the 5-year survival and the median survival time in the palliative treatment of stage IV CRC cancer patients.

Keywords: Colorectal cancer; Dendritic cells; LANEX-DC®; Immunotherapy; Stage IV; Adjuvant

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Introduction

35% of Colorectal Cancer (CRC) patients present with stage IV metastatic disease at the time of diagnosis and 20% to 50% with stage II or III disease will progress to stage IV at some point during the course of their disease [1-3]. The 5-year survival rate for stage IV CRC is less than 10% [2,3].

The combination of infusional FU/FA with either oxaliplatin or irinotecan improved efficacy, and both regimens currently are used as standard therapies in chemotherapy naive patients with CRC [4-7]. With these palliative treatments median Overall Survival times (OS) increased from approximately 5 months with optimal supportive care without chemotherapy to 13 to 21 months using the standard therapies [4-8].

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 [9]. Several studies have indicated that dendritic cell therapy is effective in treating different types of cancer [10]. Xu et al. [11] reported about a slight but not significant increase in median OS in stage IV CRC patients who underwent DC treatment in combination with cytokine induced killer cells in a small series.

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 [10]. In the following retrospective analysis, we investigated the outcome of immunotherapy with DC (LANEX-DC® - long antigen exposition dendritic cells) in the palliative treatment of CRC stage IV patients.

Patients and Methods

Patients

73 patients suffering from stage IV colorectal cancer have been vaccinated with autologous dendritic cells at our institution. The mean age was 65.1 years (39 to 88.7 years). 55 patients were male, 18 patients were female. In 50 patients colorectal cancer was first diagnosed, in 23 patient

relapse was diagnosed after colorectal cancer in the past. The metastasization status in the 73 patients was: 30/73 (41.1%) patients had liver metastases alone, 5/73 (6.8%) patients had a combination of liver and lung metastases, 8/73 (10.9%) patients had liver and peritoneal metastases, 19/73 (26.0%) has peritoneal metastases, 8/73 (10.9%) had lung metastases, one patient (1.3%) had distant lymph node metastases and 2/73 (2.7%) of the patients had local relapse following rectal amputation. 30/73 (41.1%) of the patients had rectal cancer, 43/73 (58.9%) of the patients had colon or sigmoid cancer. In 52/73 (71.2%) of the patients a palliative resection of the primary tumor was performed. 68/73 (93.2%) of the patients received palliative chemotherapy: 34/73 (46.6%) patients received 5-FU, 1/37 (1.4%) Gemcitabine, 1/37 (1.4%) FOLFIRI, and 19/73 (26.0%) FOLFOX. 13/73 (17.8%) of the patients underwent regional chemotherapy. Patient selections by performance status, liver-enzyme values, etc. were not made. Immunotherapy with DC was carried out in a median of 21 days following surgery. Per patient a mean number of 2.1 cycles of DC-therapy was performed (range: 1-15 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). LANEX-DC® (long antigen exposition dendritic cells) was produced as described recently [13]:

Peripheral Blood Mononuclear Cells (PBMCs) were isolated from 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 h 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 2 mM 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 re-suspended in fresh RPMI 1,640 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 Cell Genix, Freiburg, Germany). After 24 h, 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 1 ml 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 73 patients with stage IV CRC were treated with LANEX-DC®. Except light flu-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]. The mean observation time was 37.4 months. In five patients follow-up was lost after 3.3-39.8 months. Data of these patients were censored in Kaplan-Meier analysis. The median Overall Survival (OS) was 79.1% after one year, 38.7% after 3 years and 23.3% after five years. The median OS was 27.8 months (Figure 1a). In subgroup analyses no statistically significant differences were found concerning age or palliative tumor resection (Table 1).

Patients who received more than 2 cycles of LANEX-DC® lived significant longer than patients who received one or two cycles of

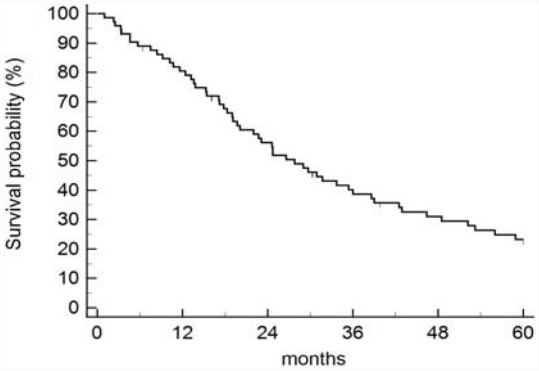

Figure 1a: Overall survival (5-years) in the palliative treatment sage IV CC patients (n=73) was 23.3% with a median survival of 27.8 months.

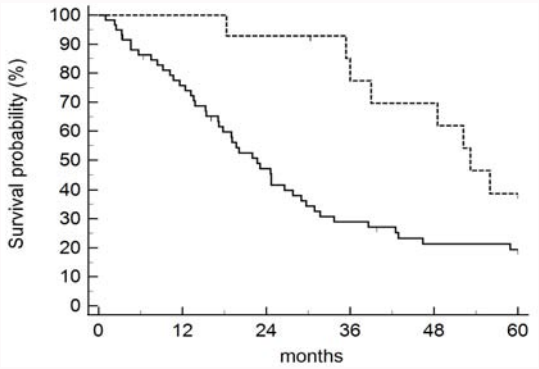

Figure 1b: Median survival in stage IV CRC patients receiving more than two cycles of LANEX-DC® (dotted line) was significantly higher than in patients who received one or two cycles of LANEX-DC® (solid line) (53.2 months *vs.* 22.7 months, p<0.02).

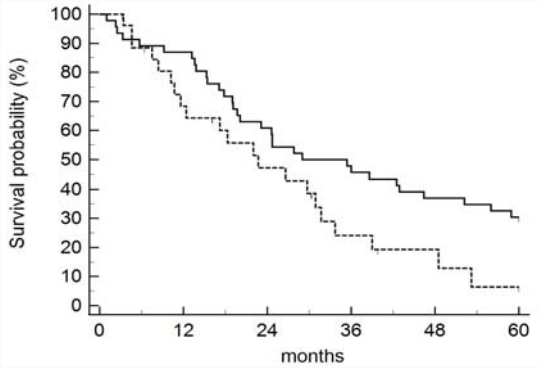

Figure 1c: Median survival in stage IV CRC patients treated with LANEX-DC® with peritoneal metastases (dotted line) was significantly lower than in patients without peritoneal metastases (solid line) (22.7 months *vs.* 30.4 months, p<0.05).

Table 1: Subgroup analyses of stage IV CRC patients receiving additional LANEX-DC®. Patients with peritoneal seedings showed a significantly shorter OS than patients without. Median OS in patients with more than 2 cycles of dendritic cell therapy was significantly higher than OS in patients with one or two cycles of LANEX-DC®.

	No of patients	Median OS (months)	Significance
All patients	73	27.8	
Age at diagnosis			
age <65	33	38.6	
age >64	40	24.7	p=0.19
Relapse status			
Yes	23	26.6	
No	50	29.0	p=0.71
Peritoneal involvement			
Yes	27	22.2	
No	46	30.4	**p=0.038**
Palliative tumor resection			
Yes	55	29.7	
No	18	17.1	p=0.27
Chemotherapeutic regimen			
5-FU/folinic acid	34	22.7	
FOLFOX / FOLFIRI	20	36.0	
regional chemotherapy	13	24.7	p=0.178
Number of cycles LANEX-DC			
1 or 2	59	22.7	
>2	14	53.2	**p=0.012**

LANEX-DC® (53.2 *vs.* 22.7 months, p=0.012, log rank test) (Figure 1b). Patients with involvement of the peritoneum lived significantly shorter than patients without (22.2 *vs.* 30.4 months, p=0.038, log rank test) (Figure 1c). With regard to the chemotherapeutic regimen, patients receiving FOLFOX/FOLFIRI palliative chemotherapy had a median OS of 36.0 months as compared to patients with other chemotherapeutic regimens or no chemotherapy (24.7 months) although this did not reach statistic significance (Table 1).

Discussion

In CRC stage IV patients the median survival without palliative chemotherapy is approximately 5 months [8]. Until a few years ago, 5-Fluorouracil (5-FU) modulated with folinic acid was the reference first line treatment option for stage IV CRC, with manageable toxicity and median survival of 10.7 to 12.3 months [6,15]. With addition of Oxaliplatin (FOLFOX) or Irinotecan (FOLFIRI) to the 5-FU/folinic acid based palliative chemotherapies median survival times in stage IV CRC patients were raised to 18.8 to 21.5 months [4-7,16,17]. In our analysis of stage IV CRC patients' additional LANEX-DC® therapy raised median survival to 27.8 months. In the subgroup of our patients receiving 5-FU/folinic acid chemotherapy the median survival was 23.7 months, in the subgroup of patients receiving FOLFOX or FOLFIRI palliative chemotherapy the median survival was 36.0 months, showing an additional increase of more than one year in median survival as compared to the data of palliative chemotherapy alone in stage IV CRC studies (see above). In patients with peritoneal involvement median survival ranges around one year with palliative chemotherapy [18]. In our cohort the median survival was 22.2 months with additional LANEX-DC® therapy pointing to an effectively even in this subgroup of CRC patients.

Interestingly patients receiving more than 2 cycles LANEX-DC® lived significantly longer than those receiving one or two cycles. These data provide evidence for a continuous additional therapy with dendritic cells during the palliative chemotherapy of CRC patients, which will be subjected in the future investigations.

In this retrospective analysis we evaluated the clinical results of 73 stage IV CRC patients who were treated in the palliative situation additionally with dendritic cells. The 5-year OS was 23.3% and the median survival was 27.8 months. These data point to a potential beneficial effect of dendritic cell therapy in the palliative treatment of stage IV CRC patients.

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