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Effectivity of Long Antigen Exposition Dendritic Cell Therapy (LANEX-DC®) in the Adjuvant Treatment of Gastric Cancer

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Abstract

Introduction: Even after surgical resection and multimodal treatment in gastric cancer the 5-year Disease Free Survival times (DFS) as well as Overall Survival rates (OS) are still below one third of the patients. Here we retrospectively analyzed the outcome of immunotherapy in the additional adjuvant treatment of gastric cancer with Long Antigen Exposition Dendritic Cell therapy (LANEX-DC®) in 16 patients who were treated at our institution (intent-to- treat-analysis).

Patients: Data were available of 16 patients. Dendritic Cells (LAEX-DC®) were produced according to a recently published protocol.

Results: Therapy was well tolerated and no serious side effects were observed. Five year DFS and OS were 62.5% and 67.5%. Interestingly, two of the patients developed recurrence of the disease more than 7 years following resection for gastric cancer.

Conclusion: We were able to show in a small cohort of patients that additional treatment with dendritic cells (LANEX-DC®) is highly effective and extends the DFS and OS in the adjuvant treatment of gastric cancer.

Keywords: Gastric cancer; Dendritic cells; LANEX-DC®; Immunotherapy; Adjuvant

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Introduction

According to the World Cancer Report gastric cancer is considered as the third leading cause of cancer-related deaths and it caused 72,300 deaths worldwide in 2012 [1]. Studies suggest that the causes of gastric cancer are related to eating habits, genetic factors, stomach diseases and other factors [2]. Due to unspecific symptoms gastric cancer is easily misdiagnosed and in most affected patients, gastric cancer progressed to the advanced stage or metastasized, and the 5-year survival rate was <20% at this stage [3]. Significant improvement in reduction of relapse rates and increased overall survival in gastric cancer was achieved by introduction of neoadjuvant chemotherapy, postoperative chemotherapy and radiotherapy. For review see Song et al. [4]. Nevertheless, despite these interdisciplinary approaches consisting of pre- and post-operative chemotherapy and high-volume center surgery the Disease-Free Survival (DFS) and the Overall Survival (OS) is still unsatisfactory with 31% and 35% [5].

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 [6]. Several studies have indicated that dendritic cell therapy is effective in treating different types of cancer [7]. Several studies have shown that additional treatment with Cytokine-Induced Killer cells (CIK)/Dendritic Cell (DC) immunotherapy is beneficial in the adjuvant treatment of gastric cancer. Disease free survival rates as well as overall survival were significantly increased [8,9]. 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 patients following surgical resection for gastric cancer.

Patients and Methods

Patients

Sixteen patients suffering from gastric carcinoma have been vaccinated with autologous

dendritic cells at our institution. Follow-up data of all patients were available. The mean age was 63.5 years (53 to 77 years). Eight patients were male, eight patients were female. Histopathological examination revealed in 10 patients' intestinal type, 3 diffuse type, 3 Adenocarcinoma (AEG). With regard to staging 4 patients showed UICC stage I, 8 patients stage II and 4 patients stage III. In 6 patients a partial resection according to Billroth I/II was performed, 10 patients underwent gastrectomy. Five Patients underwent neoadjuvant/adjuvant chemotherapy according to the guidelines. Immunotherapy with DC was carried out in a mean of 28 days following surgery.

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). Serum-pulsed LANEX-DC® (long antigen exposition dendritic cells) was produced as described recently [10].

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 resuspended in fresh RPMI 1640 supplemented with 10% serum. Again, 750 U/ml rh-GM-CSF, 500 U/ml rh-IL-4 and 100 U/ml Ca19-9 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 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 16 patients were treated with LANEX-DC® postoperatively following curative resection for gastric cancer. Except light flu-like symptoms at the day of reinjection of the dendritic cells in 3 patients (WHO II, 18.8%) no serious side effects were observed. The median observation time was 67.1 months ranging from 17.6 to 126 months. During the 5 year observation period 6 patients developed relapse of gastric cancer (1 patient liver metastases, 5 patient's local relapse/peritoneal metastases). The median time for recurrence in these 6 patients was 21.5 months ranging for 11.6 to 33.9 months.

The Disease Free Survival (DFS) and the Overall Survival (OS) was 62.5% and 81.3% after 3 years and 62.5% and 67.5% after five years (Figure 1). For the stage II/III patients the DFS and the OS were 50% and 55% respectively.

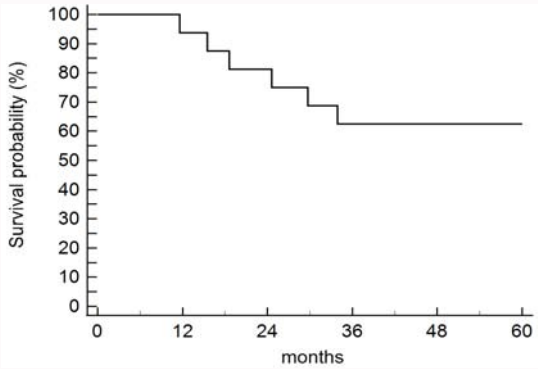

Figure 1A: Disease free survival (5-years) in the adjuvant treatment of gastric cancer patients (n=16) was 62.5%.

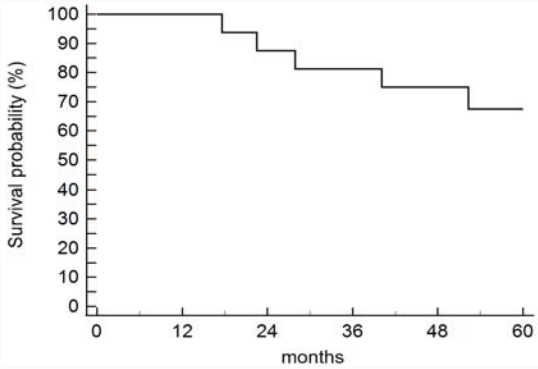

Figure 1B: Overall survival (5-years) in the adjuvant treatment of gastric cancer patients (n=16) was 67.5%.

Table 1: 5-year Disease Free Survival (DFS) and Overall Survival (OS) in the adjuvant treatment of gastric cancer using Cytokine Induced Killer cells (CIK) or Dendritic Cells (DC).

Author	Patients (n)	Immunotherapy	DFS	OS
Enzinger et al. [5]	448	none	31.0%	35.0%
Shi et al. [11]	152	CIK	28.3%	32.4%
Chen et al. [14]	226	CIK	21.0%	23.2%
Zhao et al. [15]	53	CIK	49.1%	56.6%
Gao et al. [18]	23	CIK/DC	66.0%	71.0%
own data	16	DC	62.5%	67.5%

It is noteworthy that two patients showed late recurrence 84.9 months (peritoneal carcinosis) and 89 months (liver metastases) after therapy. These late-onset relapses in gastrointestinal cancers following DC treatment, as not only seen in gastric cancer but also in colorectal cancer patients, will be addressed in a further report.

Discussion

In resectable gastric cancer 5-year DFS and OS under standard therapy according to the guidelines including chemotherapy under the given indication with 31% and 35%, respectively are still unsatisfactory [5]. In the past years many clinical studies have been conducted investigating the beneficial effects of adjuvant cellular immunotherapy in gastric cancer patients [8,9]. Most of these trials used additional cytokine-induced killer cells, showing significantly increased DFS and OS as compared to standard therapy [11-17].

For example Zhao et al. [15] showed a 5-year DFS and OS of 49.1% and 56.6% using additional CIK as compared to 24.1% and 26.8% in control patients receiving standard therapy. Gao et al. [18] showed in 23 gastric cancer patients that the additional CIK/DC therapy led to an increase of 5-year DFS and OS to 66% and 71% respectively. The results of several immunotherapeutic approaches in gastric cancer using CIK, CIK/DC or DC are shown in Table 1.

In this retrospective analysis we evaluated the clinical results of 16 patients who were treated in the adjuvant situation with dendritic cells following curative surgical resection for gastric cancer. The 5-year DFS and OS were 62.5% and 67.5%. These data are consistent with the findings of Gao et al. [18] pointing to a potential beneficial effect of dendritic cell therapy in the adjuvant treatment of gastric cancer.

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