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A Pilot Study to Analyse the Effectiveness of Dendritic Cell Immunotherapy in Ovarian Cancer

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Abstract

After breast and cervical cancers, ovarian cancer ranks third among gynaecological cancers in terms of prevalence. Those with metastatic ovarian cancer have a five-year survival rate of less than 27%. The likelihood of survival is almost 90% for people with confined or primary illness. In reality, only 20% of cancers are found at that early stage. Others were found after the tumour had already invaded the whole peritoneal cavity. Chemotherapy is ineffective against cancer cells at this stage, resulting in low survival rates and high recurrence rates. The ability of immune cells to eradicate cancerous cells is inhibited by ovarian tumours' severe immunosuppressive nature and many immune-suppressing mechanisms. In addition to conventional therapy, dendritic cell immunotherapy has been shown to be one of the most effective ways to prevent recurrence and improve overall survival by utilising the immune system's capacity to attack malignant cancers. We conducted a study on individuals with ovarian cancer while keeping in mind the tumour microenvironment and dendritic cell functionality in ovarian cancer. Individualized autologous dendritic cell immunotherapy was given to each patient. With regard to the response rate and overall survival, the study's findings and ramifications are examined.

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Introduction

After breast and cervical cancers, ovarian cancer is the third most prevalent gynaecological cancer in India. Ovarian cancer occurs in between 5.4 and 8/100000. The risk begins to rise at the age of 35 and peaks between the ages of 55 and 64 [1]. In the ovary, aberrant cell proliferation leads to the development of ovarian cancer. Every month, the ovaries generate eggs or ova, thus any malignant or mutational activity there will eventually cause it to quickly multiply, invade, and kill healthy tissues. Because the local immune cells view these malignancies as a developing foetus, they only manifest themselves in advanced stages. The majority of cases are discovered in the later stages of the disease with metastases due to late and ambiguous symptom presentation and inadequate patient screening. Neoadjuvant chemotherapy, surgery, and platinum-based chemotherapy are currently the main forms of treatment for mortality in Ovarian Cancers. However, tumours recur within 6 months after treatment, and the majority of instances are found to be in advanced stages. As a result, there is a dismal prognosis and a high death rate; 80% of patients eventually pass away from the disease. Due to the variety of original cancer cells, host immunological response to tumour activity, and tumour evasion to evade immune cell attack, there are now a number of therapy methods designed specifically to destroy tumour cells with little harm to host cells. Dendritic cell-based active immunotherapy appears to be developing as an additional therapeutic option for the majority of solid malignancies, particularly ovarian tumours.

Ovarian cancers are caused by improperly altered cancer cells that start dividing and growing out of control in the ovary, eventually producing a tumour. Cancer cells gradually encroach on nearby tissues and have the potential to migrate to other parts of the body, including the peritoneum and fallopian tubes, if they are not caught early. The most prevalent histological subtype of ovarian cancer, high grade serous carcinoma, is extremely aggressive and advances quickly. These ovarian tumours are very susceptible to the immune system. According to recent research, patients with various solid tumours, such as high-grade serous ovarian carcinoma, who have large levels of tumour-infiltrating CD8+ T lymphocytes (CTLs), infiltrated by CD 20+ B cells, a critical modulator of anticancer immunity, have significantly longer survival times (HGSC)

[2]. In the HGSC environment, these CD 8+ and CD 20+ cells frequently co-localize in lymphoid aggregates of various sizes and morphologies known as tertiary lymphoid structures (TLSs), which have the capacity to start tumour-targeting immunity [3]. In TLSs, distinct zones with CD4+ and CD8+ T cells, dendritic cells (DCs), and high endothelial venules coexist with pronounced B-cell follicles [4]. Because mature DCs choose to house TLS, they serve as a trustworthy and accurate identifier of these structures, and as a result, it is thought that they have a significant impact on the immune response at the tumour site.

Additionally, ovarian malignancies cause an immunological reaction in the body against antigens associated with tumours. These antigens linked to tumours are given as carriers or as pure preparations. The strongest immune system antigen-presenting cells that act as carriers of these tumour-associated antigens are called dendritic cells. Tumour-associated antigen-loaded DCs demonstrate beneficial antitumor responses that slow the growth of existing tumours or lengthen their time to progression (TTP) without causing any discernible damage.

CD14+ monocytes are isolated from the patient's peripheral blood for dendritic cell immunotherapy. Granulocyte macrophage colony-stimulating factor (GM-CSF) and interleukin 4 (IL-4) were used to cultivate isolated monocytes in a lab setting for six days in order to develop them into immature dendritic cells. After obtaining immature DCs, we matured/activated them for 48 hours utilising tumour-specific antigens and tumour-associated antigens. Ovarian cancer cell lines, recent tumour biopsy samples, and paraffin block allogenic/autologous tumour tissues were used to obtain whole ovarian cancer cell antigens. These fully developed DCs were stuffed with antigens from entire tumour lysate peptides. Tumour cells were made to experience necrosis by freezing and thawing or death by radiation treatment in order to increase the immunogenicity of these antigens.

In controlling the innate immune response and starting adaptive immunological responses, DCs are crucial [5]. Dendritic cells (DCs) are important immune system orchestrators and are frequently used in cancer immunotherapy. Immature DCs rest in the peripheral tissues, where they gather antigens and sample their surroundings. When the right "danger" signals are present, DCs go through a planned cell event called maturation. This is characterised by the up-regulation of cell surface molecules involved in antigen presentation and co-stimulation (such as CD80, CD86, CD40, and MHC class II), the release of pro-inflammatory cytokines like interleukin (IL)-12, and migration to lymphoid tissue [6]. Compared to other APCs including B cells, mononuclear cells, and macrophages, DCs have a more robust ability to capture, process, and deliver antigens. First and second signals to activate T cells are created by DCs. The MHC-antigen peptide-TCR complexes operate as the initial signal in the activation of certain T cells, and the costimulatory factors on the membrane of APCs act as the second signal [7]. In general, DCs collect and transform endogenous antigen into antigen peptide/MHC I molecules for CD8+ T cells and exogenous antigen peptides into antigen peptide/MHC II molecules to activate CD4+ helper T cells [8]. In general, it is believed that the key mediators of anti-tumour immune responses are CD8+ cytotoxic T cells (CTL) [3]. Major Histocompatibility Complex (HLA) class I molecules produced on ovarian cancer cells are used by these cells to show antigens [9].

A study was done on people who had been diagnosed with ovarian cancer in order to preserve the tumour microenvironment and the capacity of dendritic cells in ovarian cancer. Irrespective of the fact, patient had previously had surgery or chemotherapy, all patients got dendritic cell immunotherapy.

Materials and Procedures

At the Denvax Clinic in Vasant Vihar, a cohort study of 55 patients who received dendritic cell immunotherapy for high grade serous ovarian cancer was carried out. Dendritic cell immunotherapy was used to treat all verified cases of ovarian cancer with recurrence or residual disease following conventional therapy.

DC Vaccine Preparation

Peripheral blood was obtained from all ovarian cancer patients and mixed in a cellnute before being transferred to the laboratory, where separated monocytes were cultivated with GM-CSF and IL4 to develop into immature DCs.

Using tumor-specific antigens, immature DCs were stimulated into mature dendritic cells. Whole tumour lysate peptide antigens were loaded into mature DCs. The activated mature DCs were stored in liquid nitrogen until they were needed.

The DC vaccine was frozen to room temperature before being dissolved in 100 mL of normal saline and delivered via gradual intravenous infusion over 30 minutes. Six consecutive dosages were given at two-week intervals.

The patient was evaluated utilising

- PET response criteria in solid tumours (PERCIST) is a technique that assesses the effectiveness of treatment by monitoring metabolic changes using variations in the SUV (standardised uptake value) before and after the procedure.
- CA 125 monitoring was also carried out to forecast patient survival and treatment response.

Result

All 55 participants who were enrolled in the study had their data analysed. Ovarian cancer patients were found to have a mean age of 56.09 with standard error of mean, of which 13% had stage II, 56% had stage III, and 31% had stage IV of the disease. More than 90% of patients had high-grade serous histology, and more than 70% had tumours with poor tumour differentiation. Dendritic cell immunotherapy was administered to all 55 patients six times during a three-month period at intervals of fifteen days. Using PERCIST criteria and blood CA125 estimation, it was determined that 6 individuals defaulted throughout the course of treatment, and that 17 patients had a complete response, 14 patients had a partial response, 11 patients had stable disease, and 8 patients continued to progress with their condition. With a standard error of 2.80, the median overall survival for the total research cohort was 28.122 months. 17 people had endured without experiencing illness progression as of January 2022. There were no adverse effects or toxicities related to the immunotherapy.

Table 1: Clinical and Biological characteristics of 56 High grade serous ovarian cancers patients enrolled in the study

Variable	Overall cohort n=55
Age	
- Mean age in years ± SEM	56.09 ± 1.46
- Range	31- 80
- Standard deviation	10.87
TNM Staging	
- Stage I	0
- Stage II	7 (13%)
- Stage III	31 (56%)
- Stage IV	17 (31%)

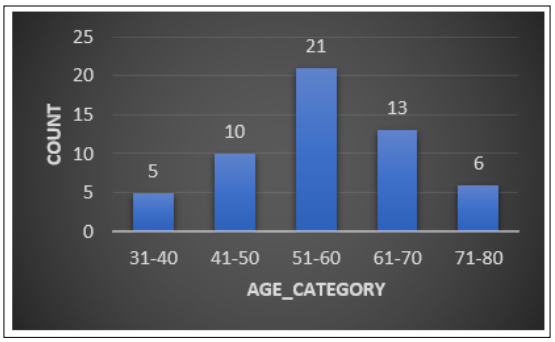


Figure 1: Age Analysis

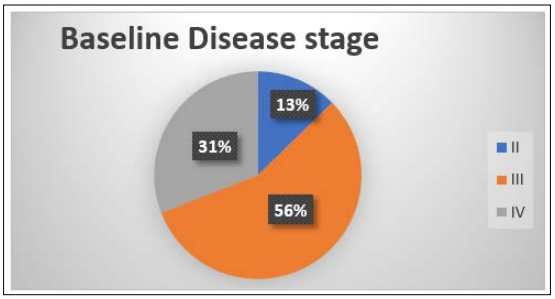


Figure 2: Ovarian cancer Stage Analysis

Table 2: Mean and Standard deviation of expected and total survival in Ovarian Cancer patients

	Expected Survival	Total Survival	Extended Survival
Mean±SEM	7.81±0.296	28.122±2.80	19.55±2.51
SD	2.07	19.64	17.5

- With 95% confidence interval, the expected survival is between 7.23 and 8.39 with margin of error of 0.58, based on 49 samples.
- With a 95% confidence interval, the total survival was between 22.6 and 33.6 with a margin of error of 5.5, based on 49 samples.
- With a 95% confidence interval, the extended survival was between 14.7 and 24.5 with an error margin of 4.9, based on 49 samples.

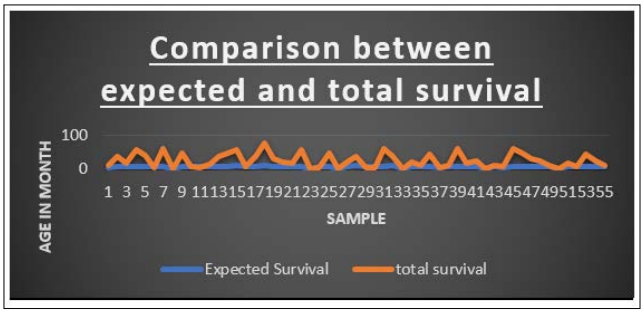


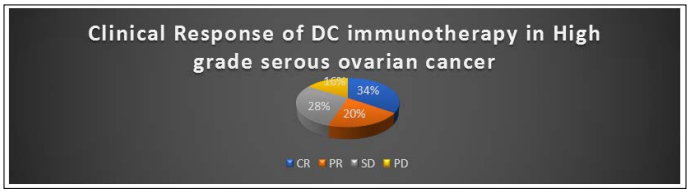
Figure 3: Comparison between expected and total survival

Table 3: Clinical Response of DC immunotherapy in High grade serous ovarian cancer

	CR	PR	SD	PD	Total
No.	17	10	14	8	49
%	34%	20%	28%	16%	100

Response rate- 54%
Cancer control ratio- 82%

Figure 4



CR- Complete response
PR- Partial response
SD- Stable disease
PD- Progressive disease

Discussion

High-grade serous carcinoma is the most prevalent histologic form of ovarian cancer, one of the most prevalent gynaecological cancers. It has been difficult to find innovative treatments for this tumour since it is so aggressive, growing quickly, and has a bad prognosis. For such patients, dendritic cell immunotherapy offers some hope. A rationale for the use of dendritic cell immunotherapy to mobilise endogenous antitumor T cells was provided by earlier cancer studies that demonstrated the effectiveness and role of CD8+T cells in anticancer immunity controlling cancer progression and a strong correlation between tumour infiltrating lymphocytes and overall survival. An immunosuppressive mechanism, VEGF and T regulatory cells, and a highly heterogeneous tumour microenvironment are all present in ovarian cancer [10]. As a result, tumour-specific T cells are unable to operate effectively, which promotes tumour growth and a poor prognosis in ovarian cancer. Both immunological and non-immunological factors, such as tumour angiogenesis, contribute to this. Ovarian tumours have a strong immune-suppressing effect. High levels of CD8+CTLS are found in high-grade serous ovarian cancer, and they colocalize as lymphoid aggregates in the tumour microenvironment. These lymphoid aggregates have impaired metabolic activity and efficacy, which promote tumour growth and shortened survival. The most potent antigen-presenting cells, dendritic cells, can activate T cells that engage T cell receptors to secrete particular cytokines and cause an anticancer cytotoxic T lymphocyte CD 8+ immune response, which results in tumour regression and improved survival for ovarian cancer patients. Dendritic cell immunotherapy may be able to increase ovarian cancer patients'

overall survival and progression-free survival, according to data from our cohort analysis of 55 patients. In this trial, we were able to demonstrate that dendritic cell immunotherapy is safe and effective for ovarian cancer patients at all stages. Both a radiological PET-CT scan and a serum CA 125 estimation make it possible to add autologous DC immunotherapy to the standard treatment for ovarian tumours, which improves both overall survival and progression-free survival. The SUV max levels and CA 125 estimation utilising the PERCIST criteria and PET-CT scans have shown positive results. We do, however, believe that larger investigations are necessary before considering its inclusion in the usual conventional treatment for ovarian malignancies.

Conclusion

Given that many patients respond well, dendritic cell immunotherapy is a promising treatment option for high-grade serous ovarian tumours. However, there is still room for improvement in the response rate, highlighting the necessity for ongoing development to maximise the impact of dendritic cells. Targetable tumour dendritic cells are becoming more and more recognised for their function in the antitumor response. To fully comprehend the function of the tumour immunological microenvironment, more study is needed.

Conflict of Interests: The authors declare that they have no conflict of interests.

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