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The safety and efficacy of ADXS11-001 with or without chemotherapy in patients with recurrent cervix cancer who have failed prior cytotoxic treatment

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A B S T R A C T

Cervical cancer, cancer in cervix the lower part of the uterus that opens at the top of vagina. It is one of the most fatal diseases that affect the women in majority of cases all over the world. It is the third most common type of cancer. Main cause for the cervix cancer is infection with Human Papilloma Virus (HPV). The viral oncoprotein E_6 complexes with Tumour Inhibitor Gene (p^{53}) and E_7 complexes with Tumour Suppressor Protein Retinoblastoma (p^{Rb}). This disrupts the cell cycle regulation leading to genomic instability and causes subsequent neoplasia. Conventional therapies for cancer such as chemotherapy and radiotherapy are characterized by poor survival rates due to tumour development of drug resistance and lack of tumour specificity resulting in undesirable side effects on healthy cells. Hence an alternate method of vaccination is preffered here. ADXS11-001 is a live attenuated vaccine consisting of *Listeria monocytogenes(Lm)* bacteria. It is bio-engineered to make it less likely to cause infection to make a special substance called E_7. Bio-engineered to secrete an antigen- adjuvant fusion protein consisting of a truncated fragment of Lm- Listeriolysin (LLO) fused to HPV-16-E_7. LLO permits bacteria to escape from phagosomes and to live intracellularly. This potentiates the class-I & II MHC antigen-processing pathway leading to specific CD_4 and CD_8 T- cell responses. Thus the drug shows it action on immune responses. ADXS11-001 was found to cause the therapeutic regression of tumours that express the HPV-16- E_7. Cisplatin is the most effective drug in cervical cancer treatment. ADXS11-001 alone & ADXS11-001 in combination with cisplatin is also administered to patients. Combination showed the better efficacy results than ADXS11-001 alone.

Keywords: Cervical cancer, Human Papilloma Virus, Viral Oncoprotein, Tumour Inhibitor gene, Tumour suppressor protein Retinoblastoma, ADXS11-001, *Listeria monocytogenes*, Listeriolysin, Phagosomes, Cisplatin.

A R T I C L E I N F O

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1. Introduction

Cancer is one of the major causes of death and it constitutes the greatest health care problem since ancient times.[1] According to the world health organization (WHO 2002) cervical cancer is said to be the world´s second deadly cancer with an estimate of about 493,243 women diagnosed with it and 273,505 dying from it per year.[2] Cervical cancer is also the world´s second most frequent among women between 15 and 44 years of age. In 2012, the World Health Organization reported an estimate of 530,000 new cases of cervical cancer and 70,000 cervical cancer-related deaths worldwide, with more than 85% occurring in low- and middle-income countries.

Globally, the cervical cancer mortality rate is very high (52%), with a 5-year survival rate of 15% for patients with advanced disease.[3,4] In patients with recurrent cervical cancer, the majority of recurrences occur within 2 years after diagnosis; prognosis and survival rates are poor. The primary causative agent of cervical cancer is the human papillomavirus (HPV). There are 13 high-risk cancer-causing HPV types, of which HPV-16 and -18 are accountable for 70% of precancerous cervical lesions and cervical cancers.[5]1 HPV-16 accounts for approximately 53% of invasive cervical cancer cases in most countries, followed by HPV-18, which accounts for approximately 13% .[6]

Improvement of patient survival remains a large unmet need and, therefore, treatment strategies that target this virus are an urgent necessity.[7] ADXS11-001 is a live, attenuated, nonpathogenic, bioengineered *Lm*-LLO immunotherapy developed for treatment of HPV-associated cancer. ADXS11-001 secretes an HPV-E7 tumor antigen as a truncated LLO-E7 fusion protein (tLLO-HPV-E7) that stimulates both innate and adaptive tumor-specific immunity tLLO-HPV-E7 is taken up by antigen-presenting cells (APCs), which are directed to induce and activate a new population of E7 antigen-specific T cells, with tumor-specific cytotoxic potential.[8,9]

Simultaneously, ADXS11-001 reduces immune tolerance within the tumor microenvironment by neutralizing regulatory T cells (Tregs) and myeloid-derived suppressor cells (MDSCs).In women with advanced cervical cancer and with recurrent/refractory cervical cancer, ADXS11-001 has been found to be well tolerated, safe, and effective.[10]

2. Materials and Methods

Ethical Consideration

This study was approved by Ethics Committee of Basavatarakam Indo-American Cancer hospital and Research Institute.

Drug Product Preparation

ADXS11-001 is formulated as a free flowing isotonic, aqueous, cream coloured suspension. The drug product is formulated at a concentration of $1\times10^{1°}$ efu/mL with a total volume of 1.2mL in each vial, at a pH of 6.8-7.8. IP injection is supplied in a 3-cc glass vial, stoppered and scaled with an aluminium seal.[11]

Cisplatin

Cisplatin is an anti-cancer ("antineoplastic" or "cytotoxic") chemotherapy drug. Cisplatin is classified as an "alkylating agent."Used to treat testicular, ovarian, bladder, head and neck, esophageal, small and non-small cell lung, breast, cervical, stomach and prostate cancers.[12]Also to treat Hodgkin's and non-Hodgkin's lymphomas, neuroblastoma, sarcomas, multiple myeloma, melanoma, mesothelioma.

Study Design

This is a Phase 1, dose-escalation, open-label multicenter study (NCT02164461). Dose-escalation is performed using the 3+3 design in 3 doses:

1.5×10^9 CFU (Dose Level 1)
2.1 x109 CFU (Dose Level 2)
3.1×10^{10} CFU (Dose Level 3)

Safety/tolerability will be assessed according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v4.03 for grading treatment-related adverse events, and by quantifying the dose-limiting toxicities (DLTs) experienced by patients who have received ADXS11-001. Computed tomography and magnetic resonance imaging will be used to assess tumor response as well as PFS as measured by Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 and immune-related RECIST (irRECIST). Immunologic effects (eg, changes in cytokine/chemokine levels) will be measured and evaluated by collection of peripheral blood for preparation of peripheral blood mononuclear cells and serum in cycle 1 of ADXS11-001 treatment. [13,14] The end of study will be defined as 1 year after the last patient's first treatment or until that patient has met a discontinuation criterion.

Criteria for Patient Selection

Inclusion Criteria:[16,17]

- Patients age 18 and older were eligible to participate in the study.
- Patients must have histologically confirmed cervical cancer that is progressive. Recurrent or advanced and is refractory to existing therapies, and have a positive response to a delayed-type-hypersensitivity (DTH) screening panel.
- Patients must have only one primary cancer.
- Patients must have an Eastern Cooperative Oncology Group (ECOG) performance status <- 2 (Karnofsky Index >60%).
- Patients must have a life expectancy greater than six months.

Exclusion Criteria

- Patients with a history of other invasive malignancies.

- Patients who have received prior radiotherapy to any portion of the abdominal cavity or pelvis other than for the treatment of cervix cancer within the last five years.
- Patients with brain metastases.
- Prior use of Gardasil or cervarix.
- Prior biologic therapy.
- A history of listeriosis.
- Pregnant women, women actively trying to become pregnant, and nursing women are excluded from this study because ADXS11-001 is a biologic agent with the potential for teratogenic or abortifacient effects.
- HIV positive patients are excluded from study.
- A positive urine test for any drug of abuse including but not limited to marijuana, cocaine, and opiates.

Immunogenicity

- The immunogenicity of two doses of ADXS11-001 was to be assessed through changes from a pre-dose baseline in parameters for anti-Tumoral response as assessed by flow cytometry cytokine analysis for IFN-y and IL-4, as well as by CD4+ and CD8+ activated cells determination. Blood samples for these analyses were collected prior to initial study dosing and at Weeks 3, 6, 12 and 16.
- Blood samples collected during the study were tested for viability. Due to the absence of cell viability, none of the samples collected were found to yield evaluable data. Additionally, baseline samples were missing for some patients.[18]

Preimmunization Evaluation

A complete history and physical exam will be performed, including height, weight, vital signs pain scale (0-10) and assessment of performance status according to ECOG criteria. Pain scale (0-10) will be performed by the Investigator/designee during all the visits to assess the pain experienced by the patients. Patients will be asked verbally about his/her pain perception, wherein0 denotes no pain and 10 denote severe pain. Same needs to be captured in the source documents.[19]

The following tests will be performed:

Complete blood count, platelet count, chemistries (calcium, phosphorus, transaminases including SGOT and SGPT, alkaline phosp [hatase, total and direct bilirubin, BUN, creatinine, albumin, total protein, electrolytes and glucose) and ECG. Tumour measurements will be obtained from the results of physical examination and radiographic studies, including CT scans, of relevant sites and documentation. All patients will undergo evaluation of the pulmonary function prior to enrolment.[20]

Vaccination Site Evaluation

The time and date, site of vaccination and number of injections will be recorded. On the day of vaccination, measurements of induration and erythema including the perpendicular diameter measurements of the injection site with the largest area of induration and erythema will be recorded within 2-4 hours after injection. Local and systemic signs and symptoms will be recorded (e.g. pruritus, urticarial, fever, pain, edema, development of adenopathy etc.) .[21]

Vaccination Day Evaluation

An interval history of any new symptoms and a physical examination will be obtained. Toxicity assessment and performance status will be recorded.

Post-Treatment Evaluations

If patients had disease progression after vaccination, they will be offered best supportive care at the discretion of the treating physician. At the completion of the vaccine course, patients will be followed at intervals not greater than every three months for one year, then telephonically every three months till death. In the phase I study of cervical cancer Metastatic, refractory (or) recurrent cervical cancer patients (stage IIIB/IV) the use of this vaccine was safe. The vaccine induced a CD8 response which is likely to be multi epitope directed and prolonged survival in a small cohort of 19 patients while maintaining excellent quality of life due to the absence of toxicity. The results of the phase I study suggested delayed tumour progression with six of 19 patients responded clinically with either partial response or stable disease. Three of 19 patients experienced adverse event (grade 1 or 2) which were judged to be potentially vaccine related. These adverse events were comprised of rash, moderate arthritic pain in joints and chest pain. Four of 19 developed some transient erythema at vaccination site. None experienced drug related serious adverse events. This phase II study was intended to conduct on 120 patients in various sites. As per our site results till date we have enrolled 4 patients with stage IIIB/IV CERVIX CANCER. Out of 4 patients 1 patient was screen failure. The remaining 3 patients have completed their total visits and are under follow up.[22,23]

3. Results and Discussions

Current recommendations for Cervical cancer patients with locally-advanced inoperable disease (stage IIIB) include platinum-based chemotherapy plus radiation therapy and chemotherapy alone for patients with metastases (stage IV). Results of these approaches are nevertheless poor, and the increase in survival is limited. The largest meta-analysis published to date concluded that chemotherapy increases the chance of 2-year survival by 10% and median survival by 53weeks. [24] A vaccination approach such as used here may be an effective means of inducing immune response in patients with non-immunogenic tumours. There is evidence that cervical cancer tumours contain tumour antigens, however, it is thought that cervical tumours are poor candidates for immunotherapy because they are poorly immunogenic and potentially immunosuppressive[52], thereby anergizing or tolerizing T-cells[53]. Cervical tumours, therefore, have not been subjected to immune attack, and hence have not been able to evolve evasive mechanisms to resist immune effector cells. Lung tumours, unlike immunogenic tumours that harbor tumour infiltrating lymphocytes, thus may succumb to killer CTLs, especially in light of the involvement of CD8 CTLs in tumour rejection in a number of model systems. This led to considering that a potentially immunogenic tumour vaccine like ours could generate an appropriate immune response.[25]

Table 1: Estimation of Haemoglobin

	Study Drug			Study Drug+ Cisplatin			
	Patients			Patients			
	I	II	Mean±SD	I	II	Mean±SD	P value
Screening	9.8	10.1	9.950± 0.212	9.8	10.4	10.100±0.424	ns
Visit 6	10.2	10.3	10.250±0.071	10.5	10.9	10.700±.283	ns
Visit 12	10.4	10.4	10.400±0.000	11.1	11.5	11.300±0.283	*
Visit 18	10.6	10.8	10.700±0.141	11.3	11.8	11.550±0.354	*

Normal range of haemoglobin is 12.00-15.00gm/dl.

Table 2: Estimation of TLC (Total Leucocyte Count)

	Study Drug			Study Drug+ Cisplatin			
	Patients			Patients			
	I	II	Mean±SD	I	II	Mean±SD	P value
Screening	4.8	5.2	5.000±0.283	5.2	5.4	5.300±0.141	ns
Visit 6	4.7	5.1	4.900±0.283	5.4	5.5	5.550±0.071	*
Visit 12	5.0	5.1	5.050±0.071	5.7	5.9	5.800±0.141	*
Visit 18	5.2	5.4	5.300±0.141	5.8	6.2	6.000±0.283	*

Normal range of TLC is 4- 10×10^3 cells/ cu.mm.

Table 3: Estimation of Lymphocytes

	Study Drug			Study Drug+ Cisplatin			
	Patients			Patients			
	I	II	Mean ± SD	I	II	Mean±SD	P value
Screening	18.2	20.1	19.150±1.344	21.2	20.6	20.900±0.424	ns
Visit 6	19.6	20.3	19.950 ±0.495	21.4	21.8	21.850±0.636	*
Visit 12	20.1	19.8	19.950± 0.212	21.1	21.6	21.650±0.071	ns
Visit 18	20.1	20.4	20.250 ±0.212	23.2	23.4	23.300±0.141	**

Normal range of lymphocytes is 20- 45%

Table 4: Estimation of Monocytes

	Study Drug			Study Drug+ Cisplatin			
	Patients			Patients			
	I	II	Mean ± SD	I	II	Mean±SD	P value
Screening	3.2	2.9	3.050±0.212	3.3	3.6	3.450±0.212	ns
Visit 6	2.9	3.1	2.950±0.212	3.7	3.7	3.800±0.141	**
Visit 12	3.0	2.8	2.900±0.141	4.1	4.2	4.150±0.071	***
Visit 18	3.0	2.9	2.950±0.071	4.8	5.2	5.000±0.283	****

Normal range of monocytes is 2- 10%

Table 5: Estimation of Neutrophils

	Study Drug			Study Drug+ Cisplatin			
	Patients			Patients			
	I	II	Mean ± SD	I	II	Mean±SD	P value
Screening	71.4	71.6	71.500± 0.141	71.2	70.8	71.000± 0.283	ns
Visit 6	71.6	71.7	71.650± 0.071	71.9	71.6	71.750± 0.212	ns
Visit 12	71.9	71.9	71.900± 0.000	72.2	72.9	72.550± 0.495	ns
Visit 18	72.1	72.3	72.200± 0.141	73.1	73.4	73.250± 0.212	**

Normal range of neutrophils is 40- 75%

Table 6: Estimation of Sgot

	Study Drug			Study Drug+ Cisplatin			
	Patients			Patients			
	I	II	Mean ± SD	I	II	Mean±SD	P value
Screening	15	16	15.500±0.707	17	18	17.500±0.707	ns
Visit 6	12	17	14.500±3.536	12	19	15.500±4.950	ns

Visit 12	17	13	15.000±2.828	12	17	14.500±3.536	ns
Visit 18	15	12	13.500±2.121	13	15	14.000±1.414	ns

Normal range of SGOT is 10 – 42 IU/L

Table 7: Estimation of Sgpt

	Study Drug			**Study Drug+ Cisplatin**			**P value**
	Patients			**Patients**			
	I	**II**	**Mean ± SD**	**I**	**II**	**Mean±SD**	
Screening	12	16	14.000±2.828	15	17	16.000± 1.414	ns
Visit 6	15	13	14.000±1.414	16	14	15.000± 1.414	ns
Visit 12	13	14	13.500±0.707	13	12	12.500± 0.707	ns
Visit 18	11	12	11.500±0.707	10	11	10.500± 0.707	ns

Normal range of SGPT is 10- 40 IU/L12

4. Conclusion

In the phase I study of cervical cancer Metastatic, refractory (or) recurrent cervical cancer patients (stage IIIB/IV) the use of this vaccine was safe. The vaccine induced a CD8 response which is likely to be multi epitope directed and prolonged survival in a small cohort of 19 patients while maintaining excellent quality of life due to the absence of toxicity. The results of the phase I study suggested delayed tumour progression with six of 19 patients responded clinically with either partial response or stable disease. Three of 19 patients experienced adverse event (grade 1 or 2) which were judged to be potentially vaccine related. These adverse events were comprised of rash, moderate arthritic pain in joints and chest pain. Four of 19 developed some transient erythema at vaccination site. None experienced drug related serious adverse events.

This phase II study was intended to conduct on 120 patients in various sites. As per our site results till date we have enrolled 4 patients with stage IIIB/IV CERVIX CANCER. Out of 4 patients 1 patient was screen failure. The remaining 3 patients have completed their total visits and are under follow up. Out of Three patient's one patient experienced serious adverse event. PI agreed that the SAE was not likely to be treatment related but due to the underlying or pre-existing disease. None of the remaining patients experienced toxicity beyond erythema and irritation at the site of injection and fever lasting for a day. Safety parameters are evaluated to find how the patients are responding to the vaccine. Main safety parameters include Haemoglobin, SGOT, SGPT, Red blood cells, White blood cells, Absolute Neutrophil count, Neutrophils and Lymphocytes. These parameters are regularly monitored during the visit procedures to find any abnormalities due to the vaccine.

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