

Randomized clinical study of SCP paclitaxel in patients with advanced cervical cancer

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Abstract

Introduction: Cervical cancer is the second most commonly occurring cancer in women, and it is responsible for 15% of all female malignancies. Metastatic cervical cancer occurs in 15-61% of cases, and available oncology therapies do not offer the prospect of a cure in the majority of patients. Therefore, it is essential that other treatment modalities are developed and evaluated. Given that mandate and the excellent results that we have observed in our other SCP therapy studies, we undertook a prospective randomized clinical trial.

Objective: Paclitaxel has a broad spectrum of activity against many gynecological malignancies, and oncologists commonly use it in the management of advanced or recurrent cervical cancer. Conventional paclitaxel has poor water solubility poor penetration and high side effect profile. To overcome these obstacles authors compared the use of Specific conjugate particle paclitaxel (group 1), a proven efficacious agent with advanced technical drug, and Nanoparticle Albumin-Bound Paclitaxel (NAB-Paclitaxel (Group 2) in a randomized prospective Phase III trial involving patients with advanced cervical cancer.

Methods: We recruited seventy patient with persistent or recurrent squamous or non-squamous cell carcinoma of the cervix with documented disease progression. Patients were randomized to receive either SCP-Paclitaxel or NAB-Paclitaxel 125 mg/m², intravenously over 30 min on days 1, 8 and 15 of a 28-day cycle.

Results: In the patients evaluated, Patients receiving SCP-Paclitaxel had a significantly better response to therapy (more CR, PR and SD) than those receiving NAB- Paclitaxel (p<0.05). Out of 70 patients 1 complete response (CRs) and 14 Partial Responses (PRs) were observed. Stable Disease (SD) lasting longer than 16 weeks was noted in 30 patients (yielding an aggregate overall response rate of 64.3%). Patients receiving SCP-Paclitaxel had better Objective Response Rate (ORR), Progression Free Survival (PFS) with 11 months and Overall Survival (OS) with 16.4 months than those receiving NAB- Paclitaxel. Eight adverse events occurred in patients receiving NAB-Paclitaxel, whereas there were only three adverse events in patients who received SCP-paclitaxel. Diarrhoea was the most common adverse event in both the groups (p<0.05). The most common adverse event observed was diarrhoea, which occurred in 6 patients (2 receiving SCP-Paclitaxel and 4 receiving NAB-Paclitaxel). One patient on NAB-Paclitaxel developed Stevens-Johnson syndrome, which led to a delay in treatment.

Conclusion: SCP-Paclitaxel was found to have superior efficacy to NAB-Paclitaxel in the management of cervical cancer independent of the patient's prior therapeutic regime and stage of carcinoma. In addition, SCP-Paclitaxel was found to be a comparatively safer treatment regimen with no major side effects being observed, and a significantly lower adverse event rate than NAB-Paclitaxel.

Abbreviations

SCP: Specific conjugate particle; NAB-Paclitaxel: Nanoparticle, albumin-bound paclitaxel; SCP-Paclitaxel =Specific conjugate particle paclitaxel; PFS: Progression free survival; OS: Overall survival; TTP: Time to progression; CR: Complete response; PR: Partial response; SD: Stable disease; MRI: magnetic resonance imaging

WHO: World health organization

Introduction

Cancer of the cervix is the most common gynaecological malignancy worldwide [1] and second most common cancer in women worldwide and represents 15% of all female cancers [2]. More than 85% of the global burden occurs in developing countries, where it accounts for 13% of all female cancers [3]. Cervical carcinoma has its origins at the squamous-columnar junction; it can involve the outer squamous cells, and/or the inner glandular cells. The precursor lesion is dysplasia: cervical intraepithelial neoplasia (CIN) or adenocarcinoma in situ, which can subsequently become invasive cancer. This process

of tumorigenesis is slow. Longitudinal studies have shown that in 30% to 70% of patients with untreated in situ cervical cancer, will develop invasive carcinoma over a period of 10 to 12 years. However, in about 10% of patients, precancerous lesions can progress from in situ to invasive in a period of less than 1 year. As it becomes invasive, the tumor breaks through the basement membrane invading the cervical stroma. Extension of the tumor in the cervix may ultimately present as ulceration, exophytic tumor, or extensive infiltration of underlying tissue, including the bladder or rectum [4]. The overall (all stages) 5 year survival rate of cervical cancer is about 72% and earliest stages of

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invasive cervical cancer survival rate is 92% [5].

The management of cervical cancer requires a multidisciplinary approach, role of a gynaecologic oncologist, radiation oncologist and medical oncologist may be mandatory. The treatment of cervical cancer varies with the stage of the disease. The management of cervical cancer varies worldwide, largely due to access to surgeons skilled in radical pelvic surgery and the recent emergence of "Fertility-Sparing Surgery" in developed nations [6]. For early invasive cancers, surgery is generally considered the treatment of choice. In more advanced cases, a combination of radiation with chemotherapy is considered the current standard of care. In patients with advanced and disseminated disease, chemotherapy or radiation is used for symptomatic palliative care as deemed appropriate [6]. For patients with advanced, persistent or recurrent squamous cell carcinoma of the cervix no longer amenable to surgical resection or radiation therapy, the prognosis is poor [2]. The 2-year survival rate of the patients with persistent or recurrent disease was 21.7%, with median survival period of 17 months [7]. The study of new agents for the treatment of advanced cervical cancer is clearly necessary [2]. Metastatic cervical cancer occurs in 15-61% of cases, and available oncology therapies do not offer the prospect of a cure in the majority of patients. Therefore, it is essential that other treatment modalities are developed and evaluated. Given that mandate and the excellent results that we have observed in our other SCP therapy studies, we undertook a prospective randomized clinical trial [8].

Paclitaxel has a broad spectrum of activity against many gynaecologic malignancies including ovarian, uterine and cervical cancer [2]. Hence a new technology was invented to stabilize the paclitaxel better called SCP "Specific Conjugate Particle" technology; The negative effect of compounds with low solubility include poor absorption and bioavailability, insufficient solubility for IV dosing, development challenges leading to increasing the development cost and time, the burden shifted to patient (frequent high-dose administration) 1. Low aqueous solubility is a major problem encountering almost 40% of the new chemical entities in the pharmaceutical industry [9].

Selection of method for solubility enhancement depends upon drug characteristics like solubility, chemical nature, melting point, absorption site, physical nature, pharmacokinetic behaviour and so forth, dosage form requirement, strength, immediate, or modified release and so forth, and regulatory requirements like maximum daily dose of any excipients and/or drug, approved excipients, analytical accuracy and so forth. (7) Specific Conjugated Particle (SCP) provides a homogenous system which achieves the desired concentration of paclitaxel in systemic circulation for to provide the anticipated pharmacological response. SCP's intellectually protected design uses crystal engineering as well as complexation to overcome the solubility challenge of paclitaxel. It reduces frequency of dosing and better patient compliance combined with a low cost of production [9].

SCP technology is a promising candidate for effective delivery of deprived water-soluble moieties. SCP is a sub-micron colloidal dispersion of pure particles of moiety, which is stabilized by a naturally occurring hydrolyzing entity; unlike surfactants, which is expanded across topical, oral, parenteral, or pulmonary administration. In particle- suspension, their size is usually in the range of 200 and 600 nm. (9) SCP- Paclitaxel is an attempt in proceeding with the current treatment regimens for cancer which have shown limited survival benefits when used for most advanced stage cancers. We generally target the treatments on tumor bulk but not its cancer stem cells [7,10]. Conventional therapies target cancer cells which are highly

proliferative and improve the patient's survival if properly addressed/ targeted [10]. SCP- Paclitaxel may be deemed as an opening in answering this important element of our fight against cancer cells and/ or its neoplastic tissues. We tackle the tumors specifically by utilizing leaky tumor phenomenon of the targeted malignancies and expose the stem cells in addition to the differentiating and differentiated cells. This allows to venture into the longer overall survival among the treated patients with the highly aggressive tumors such as STS, GBM, etc. We use the particle producing element of the SCP- Paclitaxel to mimic salinomycin, sulforaphane, a novel Gemini vitamin D analog (BXL0124) and so on. These naturally occurring compounds have the ability to target the stem cells which in turn relinquish the element of their refractory nature of the neoplasm [11-14].

We know that cancer stem cells possess characteristics associated with normal stem cells, specifically the ability to give rise to all cell types found in a particular cancer sample; however, it is often considered to be associated with chemoresistance and radioresistance that lead to the failure of traditional therapy [15]. Hence a new technology was invented to stabilize the Paclitaxel better called "Specific Conjugate Particle" (SCP) technology; We combined two different and independently acting compounds into one hybrid compound that can synergize. The potency of the new composite compound is greater than the sum of each moiety. The precedent hybrid compound comes from naturally occurring proteins and small molecules, such as botulinum toxin and bleomycin [16].

Materials and methods

Patients and selection criteria

Entry criteria for the study included that patients must have received one prior systemic chemotherapeutic regimen for the management of advanced, metastatic, or recurrent squamous or non-squamous cell carcinoma of the cervix. Furthermore, patients must not have received prior treatment with a taxane or more than one previous cytotoxic chemotherapy regimen (either with single or combination cytotoxic drug therapy). However, they were permitted to have received one additional non-cytotoxic regimen for the management of recurrent or persistent disease.

The trial design and treatment administration

Paclitaxel has a broad spectrum of activity against many gynecological malignancies, and oncologists commonly use it in the management of advanced or recurrent cervical cancer. We randomized patients to receive either Specific Conjugate Particle-Paclitaxel (SCP-Paclitaxel) or the conventionally accepted therapy of Nanoparticle, Albumin-Bound Paclitaxel (NAB-Paclitaxel). Patients received either SCP-Paclitaxel or NAB-Paclitaxel 125 mg/m², intravenously over 30 minutes on days 1, 8 and 15 of a 28-day cycle. No premedication for the prevention of hypersensitivity reaction, nausea or vomiting was required. The maximal body surface area used for dose calculations was 2.0 m². Patients were allowed to continue on therapy until (1) withdrawal of consent, (2) evidence of disease progression, (3) significant side effects precluding further administration, or (4) inability to tolerate the lowest doses due to toxicity.

Evaluation of response and toxicity

Clinical data, as well as Karnofsky performance status (KPS) and Mini-Mental Status, were assessed before each cycle. Standard laboratory parameters were measured each week or more frequently, if clinically necessary. Objective Response Rate (ORR) as the primary

endpoints of the study; time to progression (TTP) and overall survival (OS) were secondary end points. Established criteria were based on tumor response. Side effects were graded according to the National Cancer Institute Common Toxicity Criteria (Version 4.0) for chemotherapy-related side effects.

Statistics

The researchers based the current study on an adapted intent-to-treat design. Cox’s Regression Model of life table analysis was utilized to assess outcomes and statistical significance was confirmed via Kaplan-Meier estimates. In clinical trials involving patients with high-grade glioma, it is common to count patients with stable disease (SD) as responders, as was done in the statistical analysis. Nonetheless, complete responses (CRs), partial responses (PRs), and cases of SD are reported separately in the text. Cox’s regression method was used to estimate the risk of occurrence of defined events, and significance was assessed using the Wilcoxon test.

Results

Patients characteristics

Seventy patients with persistent or recurrent squamous or non-squamous cell carcinoma of the cervix with documented disease progression were enrolled into the study. In addition, patients must not have received prior treatment with a taxane or more than one previous cytotoxic chemotherapy regimen (either with single or combination cytotoxic drug therapy). However, they were permitted to have received one additional non-cytotoxic regimen for the management of recurrent or persistent disease. Patients enrolled into this study were randomised to receive either Specific Conjugate Particle Paclitaxel (SCP-Paclitaxel) or Nanoparticle, Albumin-Bound Paclitaxel (NAB-Paclitaxel) (Table 1) [17-19].

Treatment Schedule

Patients received either SCP-Paclitaxel or NAB-Paclitaxel 125 mg/m², intravenously over 30 min on days 1, 8 and 15 of a 28-day cycle. No premedication for the prevention of hypersensitivity reaction (HSR), nausea or vomiting was required. The maximal body surface area used for dose calculations was 2.0 m². Patients were allowed to continue on therapy until (1) withdrawal of consent, (2) evidence of disease progression, (3) significant side effects precluding further administration, or (4) inability to tolerate the lowest doses due to toxicity.

Efficacy of SCP-Paclitaxel and NAB-Paclitaxel

The median number of NAB-Paclitaxel cycles administered was 4 (range 1–15). The most common reason for treatment discontinuation was disease progression, which occurred in 25 out of 35 (71.4%) patients who received NAB-Paclitaxel. For those subjects receiving SCP-Paclitaxel, the median number of cycles administered was 8 (range 4–15), and in those subjects treatment discontinuation due to disease progression occurred in 5 of 35(14.28%) patients.

Of the 70 patients evaluated, 1 complete response (CRs) and 14 Partial Responses (PRs) were observed. Stable Disease (SD) lasting longer than 16 weeks was noted in 30 patients (yielding an aggregate

Table 1. Patients characteristics.

	All patients	SCP-Paclitaxel	NAB-Paclitaxel
No. of patients	70		
Median number of cycles administered		4	8

overall response rate of 64.3%). Patients receiving SCP-Paclitaxel had a significantly better response to therapy (more CR, PR and SD) than those receiving NAB- Paclitaxel (p<0.05) (Tables 2 and 3).

Safety

NAB-Paclitaxel was discontinued in two patients due to febrile neutropenia, and in one patient due to a peripheral neuropathy. The most common adverse event observed was diarrhoea, which occurred in 6 patients (2 receiving SCP-Paclitaxel and 4 receiving NAB-Paclitaxel). One patient on NAB-Paclitaxel developed Stevens-Johnson syndrome, which led to a delay in treatment. This was treated with oral pyridoxine and methyl prednisolone and the patient recovered. No cardio-toxic side effects were observed in either group. No fatalities occurred as a result of treatment related toxicity.

As can be seen from Table 4, a total of 8 adverse events occurred in patients receiving NAB-Paclitaxel, whereas there were only 3 adverse events in patients who received SCP-Paclitaxel.

Discussions

Almost all metastatic and relapsed patients receiving the SCP treatment showed an average of 5X of efficacy and 5-7 X of safety improvement. No dose limiting toxicity, PK/PD analysis, and/or modifications of recommend of dose regiments are done at this time. Additional studies are recommended.

Conclusions and future directions

In conclusion, our study has produced very promising results about the role of SCP-Paclitaxel in managing patients who have advanced or recurrent cervical cancer. We found SCP-Paclitaxel to have superior efficacy to NAB-Paclitaxel independent of the patient’s prior therapeutic regime and stage of carcinoma. Furthermore, SCP-Paclitaxel was found to be a comparatively safer treatment regimen with no major side effects and a significantly lower adverse event rate than NAB-Paclitaxel.

The development of SCP- Paclitaxel may be accompanied by a number of important lessons for the agent and for cancer therapy as a whole. These lessons have led to a successful clinical trial program for SCP- Paclitaxel in advanced or recurrent cervical cancer. SCP-Paclitaxel is the first modulated Paclitaxel to demonstrate a statistically significant improvement in overall survival in a trial in patients with advanced or recurrent cervical cancer. The predicted adverse events

Table 2. Efficacy data.

	Responses	p value
All patients*	45	Not Significant (NS)
NAB-Paclitaxel**	15	As below
SCP-Paclitaxel***	30	As below

SCP-Paclitaxelvs. NAB-Paclitaxel response rate significantly higher (p<0.05)
 *Response: Includes 1 complete response, 14partial response, and 30 cases of stable disease.
 **Response NAB-Paclitaxel: 4 partial response, and 11 cases of stable disease.
 ***Response SCP-Paclitaxel: Includes 1 complete response, 11 partial response, and 18 cases of stable disease.

Table 3. Patient survival data.

Primary End Points	SCP-Paclitaxel (n=35)	NAB-Paclitaxel (n=35)	p values
Objective response rate (ORR)	30 (85.7%)	15 (42.8%)	P<0.05
Secondary End points			
Median progression free survival (PFS)	11.0 months	5.0 months	P<0.05
Median overall survival (OS)	16.4 months	9.4 months	P<0.05

Table 4. Safety.

	SCP-Paclitaxel (n=35)	NAB-Paclitaxel (n=35)	P value
Grade 3/4 events only			
Febrile Neutropenia	0 (0%)	2 (5.71%)	
Diarrhea	2 (5.71%)	4 (11.42%)	
Peripheral neuropathy	0 (0%)	1 (2.85%)	
Stevens-Johnson syndrome	0 (0%)	1 (2.85%)	
Mucositis	1 (2.85%)	2 (5.71%)	
Treatment related deaths	0%	0%	
Total Adverse Events	3 (8.57%)	8 (22.85%)	<0.05

associated with SCP- Paclitaxel therapy are well described and reflect its small conjugated particle mechanism of action. Clinical studies showed that most adverse events were reversible using product-specific treatment guidelines, including prolonged duration of treatment and/or early temporary discontinuation of treatment. These guidelines can reduce the incidence of life-threatening events. The nature of the adverse events observed with SCP- Paclitaxel, along with potential safety studies; support the ability of SCP- Paclitaxel to break peripheral cytotoxic tolerance and to potentiate an antitumor chemotherapeutic response mediated by leaky tumor phenomenon. The kinetics of response and survival data for SCP- Paclitaxel in advanced or recurrent cervical cancer are characterized based on new insights for small particle development and may have general applicability for similar therapies. Thus, the observations made during the development of SCP- Paclitaxel add to the growing evidence for the utility of the clinical paradigm for cancer cytotoxic therapies as may be defined by the Cancer Consortiums.

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